World Psychiatry

OFFICIAL JOURNAL OF THE WORLD PSYCHIATRIC ASSOCIATION (WPA)

Volume 23, Number 2 *June 2024*

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ISSN 1723-8617

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World Psychiatry

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3. Fraeijs de Veubeke B. Displacement and equilibrium models in the finite element method. In: Zienkiewicz OC, Hollister GS (eds). Stress analysis. London: Wiley, 1965:145-97.

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***World Psychiatry* is indexed in PubMed, Current Contents/Clinical Medicine, Current Contents/Social and Behavioral Sciences, Science Citation Index, and EMBASE.**
All back issues of *World Psychiatry* can be downloaded free of charge from the PubMed system (http://www.ncbi.nlm.nih.gov/pmc/journals/297).

Dehumanization and mental health

Dehumanization is a fearsome word, calling to mind the gravest atrocities of the past and present. People seen as less than human have suffered and suffer violence, deprivation, exclusion and dispossession, and that suffering has been and is routinely ignored or minimized. However, although dehumanization is usually understood as an extreme phenomenon confined to wars, genocides and conquests, it falls on a spectrum. Two decades of social psychological research have shown that it has significant repercussions in everyday life[1].

The burgeoning literature on dehumanization offers three key insights. First, dehumanization ranges from blatant and verbalized to subtle and unconscious: people can be explicitly likened to animals, but also implicitly denied fundamental human qualities such as rationality, self-control and complex emotions. Second, dehumanization takes varied forms, from seeing others as bestial or robotic, to rejecting their individuality or agency, to failing to spontaneously grant them minds. Third, although dehumanization often accompanies negative views of others, it is psychologically and even neurally distinct from prejudice. Seeing people as less than fully human is not the same as disliking them. We can dehumanize those about whom we are indifferent, not only those we hate. Indeed, studies of close relationships show that we can subtly dehumanize those we love.

The vast literature on stigma reveals how people with mental illness are often viewed negatively by the general public, pictured as dangerous, blameworthy and shameful, with adverse implications for equity, well-being and recovery. It has recently become clear that, in addition to these negative perceptions, they are often also denied humanity. People are seen as less human when they receive mental rather than physical illness labels, and people with mental illnesses – especially schizophrenia and addictions – are even more blatantly dehumanized than some vilified ethnic or religious minorities[2].

Dehumanizing attitudes to the mentally ill are not confined to the public, but can also be held by mental health professionals. Researchers have begun to document the causes and consequences of these attitudes. One contributing factor is emotional self-preservation: professionals may dehumanize patients as a way to protect themselves against emotional exhaustion and distress[3]. The anticipation of emotional demands may motivate professionals to deny humanity to others and result in the withholding of empathy and care.

Studies like these shine a new light on burnout, one of whose primary manifestations is the loss of empathy for others. In clinical settings, this dehumanization-like tendency may lead professionals to disengage from patients, failing to appreciate their emotional experience and reducing them to their diagnosis. Adverse working conditions that foster burnout, such as excessive workloads and organizations that treat employees as interchangeable cogs in an industrial machine, can lead mental health professionals to dehumanize patients, with the adverse effects on clinical care that burnout researchers have documented. One study found that psychiatric nurses who felt unsupported by their organizational superiors were more likely to experience burnout and depression as well as to dehumanize their patients (e.g., showing a greater willingness to bypass their consent)[4].

People who seek mental health treatment need not be denied humanity on the basis of their illness to suffer the impacts of dehumanization. Dehumanizing perceptions of racial minorities might contribute to racial disparities in mental health diagnosis and treatment, such as significantly elevated rates of chemical sedation in African American patients presenting to emergency departments with psychiatric disorders[5], just as race-based dehumanization contributes to harsh discipline in criminal justice and educational settings.

People who believe they are being denied humanity by others typically respond negatively. Just as believing that one is dehumanized based on one's race or political views has been shown to generate antagonistic reactions, so patients' engagement with psychiatric treatment may be undermined by experiences of dehumanization from demeaning media representations, dismissive interactions with professionals, and deindividuating encounters with the health care bureaucracy[6].

Dehumanizing perceptions can also be internalized rather than resisted. People who believe that others see them as less than human may come to "self-dehumanize". This phenomenon may have significant clinical implications. A study of patients with severe alcohol use disorders found that those who self-dehumanized more had lower self-esteem and engaged in less functional coping[7]. Research such as this indicates how dehumanization can create vicious cycles that compromise therapeutic aims. Being dehumanized can lead to feeling dehumanized, which can sabotage treatment.

Being perceived as less than human may exacerbate an existing mental illness, but dehumanization might also be a risk factor for developing it. Indeed, studies point to adverse effects of dehumanization which are known psychiatric vulnerability factors. Being perceived as less than human increases people's feelings of social exclusion and also decreases others' willingness to help and show empathy[1]. The resulting social disconnection may amplify risk especially for internalizing and substance use disorders.

In addition to reducing social connection, dehumanization increases tendencies to actively harm people and to tolerate harm perpetrated by others. People with stronger tendencies to dehumanize others are more likely to engage in bullying; men who dehumanize women are more prone to sexual violence and harassment; and people who dehumanize their opponents in ethnic conflicts are more likely to support violent actions towards them[1]. Exposure to violence is a significant psychiatric risk factor, and dehumanization fosters it. At a more systemic level, dehumanization based on race, social class, and immigrant status may reinforce the public acceptance of social disadvantage and economic hardship, known contributors to mental health inequities.

The concept of dehumanization has proven to be a fruitful one for thinking about many forms of interpersonal and intergroup conflict. It complements more familiar constructs such as prejudice, stigma, stereotyping and discrimination by focusing on whether we perceive and treat others in ways that recognize our common humanity. Failures to do so have now been demonstrated in perceptions of diverse social groups, and their destructive implications are increasingly well understood. Research on dehumanization in the psychiatric realm is in its infancy, but strongly suggests that failures to fully humanize people with mental illness are widespread and have significant consequences.

How dehumanization related to mental illness should be addressed is not a straightforward issue. At a population level, a cultural change is required for public perceptions of mental illness to become more humanizing. The promotion of dimensional models may lead people with mental illness to be seen as less drastically "other". Some aspects of dehumanizing media representations of mental illness have measurably declined in recent decades[8].

It is equally important to lessen dehumanization in clinical practice[9]. Dehumanization can be reduced by enhancing empathy in professionals, through selection and training, while recognizing that empathy and problem-solving can sometimes be in conflict, and by promoting face-to-face contact between professionals and patients despite the growing intrusion of medical technologies. Dehumanization can also be diminished by ensuring that patients and professionals are presented as individuals with uniquely identifying attributes, boosting patients' sense of agency by increasing their say over treatment, and attenuating the real and perceived dissimilarity between patients and professionals.

The goal of humanizing care, within and beyond the mental health field, should be widely recognized and shared, and concrete strategies to address this goal should be identified and implemented. In addition to this, the impact of dehumanization on mental health at the population level should become a more explicit and specific focus of research.

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DOI:10.1002/wps.21186

Reflections on philosophy of psychiatry

In this issue of the journal, Stein et al[1] summarize the current status of philosophy of psychiatry, focusing on several issues in the areas of nosology, psychiatric science and the mind-body problem.

I agree with their favorable view of "soft naturalism" as an appropriate conceptualization of psychiatric diagnostic categories. "Hard" naturalism, expecting clear boundaries and essences, which applies to some entities in science (e.g., elements of the periodic table) is clearly inappropriate for psychiatric disorders. Our disorders are "fuzzy" and do not have essences.

Do psychiatric disorders exist in the world to be "discovered" or do we "create" them? Although I favor the former position, historical work suggests some skepticism. If Kraepelin went into zoology, like his older brother, would someone else have described dementia praecox and manic-depressive illness in the same terms? Many clinicians were working, over the 19th century, to sort out the diagnostic space of mood and psychotic disorders[2]. Something resembling our current views would likely have evolved without Kraepelin, but how similar would it have been?

Psychiatry has long believed that the next scientific revolution – be it brain pathology, Mendelian genes or monoamine neurotransmitters – would solve the problem of psychiatric disorders by discovering mono-causal "essentialist" explanations. This is a regrettable, recurrent pipe-dream of our profession. Ironically, near the beginning of the evolution of psychiatry (early 19th century), we confronted general paresis of the insane. This has been the greatest success story of our science, but left us with an unrealistic expectational set that we cannot repeat for our remaining syndromes.

With some rare exceptions, psychiatric disorders are highly multi-causal "all the way down". It is therefore unrealistic of us to express impatience that DSM has not yet produced an etiology-based diagnostic system. Despite all the advances in brain imaging and molecular genetics, we still remain ignorant at a basic level about the causes of our disorders. This is not likely to change anytime soon. Indeed, advances in molecular genetics are pointing out how hard this will be, aptly called "the curse of polygenicity".

My view of the role of values in psychiatric nosology is more restricted than that advocated by Stein et al. The most important value that enters into the DSM review process is the prioritization of potential validators. We broadly agree now that diagnostic change should, in so far as possible, be empirically based. Revised sets of criteria for a disorder have to perform better than their predecessors on real-world data. But how to decide what kind of performance should be prioritized? Once you know what you want your diagnoses to do, it becomes more possible to at least approximate a full-bore data-driven approach. The current system, with many different validators of uncertain weights, is problematic[3]. The DSM Review Committees have a much more difficult job than those who evaluate randomized controlled trials for the US Food and Drug

Administration, in which drug response is the only relevant variable.

I also agree with Stein et al's emphasis on the importance of pluralism in psychiatry. As a field, we have multiple legitimate scientific perspectives on our disorders, their etiology, and their treatment. The need for pluralism results from the multi-causal nature of most of these disorders. However, I have a concern about "undisciplined" pluralism: it is at risk for degenerating into an anti-scientific "let a 1,000 flowers bloom" perspective. To sit at the pluralist table, hard empirical work is needed. Correlations are not enough. Designs that allow causal inference are critical. Our thresholds need to be high, because the field of mental health attracts a wide variety of theorists, some of whom are little constrained by the problems of empirical evidence. I advocate for a "hard-nosed" pluralism. I have also been long concerned with how often people enter into our field with a research agenda highly influenced by strong *a priori* ideological commitments. This is, I have thought, partly because of our immaturity as a field, but partly because many of our research areas touch on core assumptions about the nature of being human.

I also appreciate Stein et al's concerns on how to put together the multiple perspectives on psychiatric disorders. It is too easy for our highly specialized researchers to dig deeply into their own corner of the etiologic space of psychiatric illness for an entire career and never look up. In fact, our funding system encourages such specialization. I favor a brand of "pluralism" not discussed by Stein et al: "integrative pluralism"[4]. This brand suggests that, every once in a while, it is incumbent on a scientist to come out of his/her hole and spend some energy trying to integrate his/her findings with at least those of adjacent perspectives.

A comment on reduction is warranted here. I do not consider it a dirty word. Indeed, the increasing merger of molecular genetics and molecular neuroscience to uncover risk pathways from genetic variants to psychiatric disorders is among the most exciting in our field. More power (and funding) to them would be advisable. My objection is to those reductionists who argue that their approach is the only way. "Reductive hubris" has been harmful to us at several historical phases of our discipline. Certainly, all research pathways for psychiatric disorders are not equal. But psychological and social interventions have proved their value for a number of our disorders, bringing me back to the arguments above about multi-causality.

In contrast to the above questions – which exist largely within the philosophy of science – the mind-body problem is fundamentally a metaphysical one. While innately fascinating, the insights gained compared to the effort needed to wend one's way through the metaphysical thickets in this area have, for me, been disappointing over the years. I will therefore only make a few brief and personal comments. Philosophers ponder the mind-body problem. Psychiatrists live it. The best metaphor I have heard to describe many psychiatrist-patient encounters, where the good clinician has to switch back and forth between seeing his/her patients as minded and brained, is "binocularity"[5]. As we can see depth in the world through our two eyes, we see more deeply into our patients by seeing them through two different lens – brained and minded.

I am a non-reductive materialist. I am not sure that this is a coherent position, but it is the best I can come up with. It means roughly that I do not, for my scientific work, assume that mind can exist independent from brain. Indeed, my mind is instantiated in my brain. But the mind-brain system is an interactive one – although I cannot explain how that works. Mind is a level central to the psychiatric profession. The concept of a mind-less psychiatry is oxymoronic to me. Indeed, I suggest that the tensions between mind-based and brain-based perspectives have been definitional for our history[6]. And I believe in top-down causation. Important things "happen" at the level of mind that are sometimes of great psychiatric significance[7].

In conclusion, it is heart-warming to see a prominent psychiatric journal give space to this wide-ranging and thoughtful essay. The nature of psychiatry is such that all researchers and clinicians bring to their work a range of philosophical assumptions. The only question is whether, at some point in their career, they take time and energy to examine some of them and decide whether any of them might need revision.

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DOI:10.1002/wps.21187

From “online brains” to “online lives”: understanding the individualized impacts of Internet use across psychological, cognitive and social dimensions

Joseph Firth[1,2], John Torous[3], José Francisco López-Gil[4,5], Jake Linardon[6], Alyssa Milton[7,8], Jeffrey Lambert[9], Lee Smith[10], Ivan Jarić[11,12], Hannah Fabian[1], Davy Vancampfort[13,14], Henry Onyeaka[15], Felipe B. Schuch[16,17,18], Josh A. Firth[19,20]

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In response to the mass adoption and extensive usage of Internet-enabled devices across the world, a major review published in this journal in 2019 examined the impact of Internet on human cognition, discussing the concepts and ideas behind the “online brain”. Since then, the online world has become further entwined with the fabric of society, and the extent to which we use such technologies has continued to grow. Furthermore, the research evidence on the ways in which Internet usage affects the human mind has advanced considerably. In this paper, we sought to draw upon the latest data from large-scale epidemiological studies and systematic reviews, along with randomized controlled trials and qualitative research recently emerging on this topic, in order to now provide a multi-dimensional overview of the impacts of Internet usage across psychological, cognitive and societal outcomes. Within this, we detail the empirical evidence on how effects differ according to various factors such as age, gender, and usage types. We also draw from new research examining more experiential aspects of individuals’ online lives, to understand how the specifics of their interactions with the Internet, and the impact on their lifestyle, determine the benefits or drawbacks of online time. Additionally, we explore how the nascent but intriguing areas of culturomics, artificial intelligence, virtual reality, and augmented reality are changing our understanding of how the Internet can interact with brain and behavior. Overall, the importance of taking an individualized and multi-dimensional approach to how the Internet affects mental health, cognition and social functioning is clear. Furthermore, we emphasize the need for guidelines, policies and initiatives around Internet usage to make full use of the evidence available from neuroscientific, behavioral and societal levels of research presented herein.

Key words: Internet, social media, cognition, mental well-being, attention, memory, social functioning, addiction, artificial intelligence, culturomics

(World Psychiatry 2024;23:176–190)

The digital revolution has transformed almost every aspect of our daily lives. From our leisure activities, to professional endeavors, to social interactions, the Internet has embedded itself deep in the core of contemporary lifestyles worldwide. What is less apparent, however, is the potential impact of this pervasive technological adoption on the human mind itself. In 2019, this topic drew the attention of a paper in this journal[1], which reviewed the literature around how the Internet may be influencing our attentional capacities, memory processes and social cognition.

Since the publication of those initial findings, the integration of the Internet into societal fabric has continued to expand. As reflected by a Pew Research Center’s analysis[2], there has been a consistent growth in smartphone ownership and an ongoing upward trajectory in global Internet utilization, with nearly 50% of youth describing themselves as “always online” in 2023. Recent studies have also shown how these trends have accelerated in the context of the COVID-19 pandemic[3], which produced a marked shift in the population’s reliance on digital technologies for work and social communication, further entrenching digital technology into daily routines.

Along with observing even further adoption, we are also learning more about *how* people are spending their time online, which is ever-changing. For instance, there is an ongoing shift towards online media (primarily music and video), away from traditional media broadcasting. Radio networks lose ground to online music streaming and podcasts, with the average user spending around 100 min each day listening to music via apps, and a further hour listening to podcasts[4]. Online video platforms have grown considerably in recent years, now rivalling traditional television in terms of total viewing time among users[5], and YouTube has become the most popular social media website[2].

Within this, the nature of online videos has shifted, due to innovations in the delivery of short-form video content following the meteoric rise of TikTok, which gained global fame after amassing over a billion downloads in 2019[6]. In turn, Instagram, Facebook and YouTube have introduced similar short-form video features, such as “reels” and “shorts”. Collectively, this shift has profoundly influenced the way in which online videos are produced and consumed worldwide.

There is also a concomitant change in the perceived societal value attached to online entertainment. For instance, a university in Ireland offers now a four-year bachelor's degree course in content creation and "influencing"[7].

However, the latest global data from 2023[4,5] show that social media continue to represent the largest portion of Internet usage in the modern digital landscape, with working-age users spending over 2.5 hours daily on various platforms, accounting for 38% of their total time. While 24% of teens reported being online constantly in 2015, that number rose and remained at 46% in both 2022 and 2023[2]. Accordingly, much of the evolving scientific and public debate around the psychological and societal impacts of the Internet has focused on this facet of the online world, with numerous recently emerging national health policy documents and clinical guidelines[8,9], along with a mass of new academic literature across all aspects of how the Internet may influence mental health, cognition and sociality.

In response to recent changes in our perceptions and understanding around Internet usage, this paper updates the 2019 review[1], expanding upon the leading hypotheses around how the Internet can impact upon mental, cognitive and social health. We take into account the latest data from both quantitative and qualitative research, to shed new light on the experiential aspects of how Internet usage can affect individuals' mental states, and elucidate the putative sociodemographic, psychological and behavioral factors that may mediate this.

PSYCHOLOGICAL IMPACTS OF INTERNET USE: A PERSONALIZED PERSPECTIVE

The potential impact of Internet use on mental health continues to permeate mainstream media and public consciousness, particularly with regards to social media and youth. For instance, the US Surgeon General's 2021 statement on adolescent mental health[9] drew considerable attention towards this, focusing mostly on the negative impacts of social media on mental health, and even pointing towards this as a suspected driving factor of the dramatic increase in suicide rates and self-harm seen among US young people in recent years. Additionally, an ongoing lawsuit brought by several US states against Meta, the company which owns Facebook, alleges that the company knowingly harmed the physical and mental health of young users by utilizing psychologically manipulative features on its platforms[10].

On the other hand, major mental health advocacy groups, such as the US National Alliance on Mental Illness (NAMI), while recognizing the potential psychological risks of social media, also highlighted some real-world benefits observed in certain contexts. In particular, the in-depth discussions about mental health which can unfold on these platforms are thought to be reducing stigma, improving understanding, and providing a valuable source of peer support for some people[11]. As the public debate on this issue inevitably continues, it is necessary to re-evaluate the empirical evidence regularly, in order to inform our understanding and public health advice/initiatives.

Overall, recent studies have indicated that the potential negative impacts from Internet use (and particularly social media) are not heavily linked to the amount of time spent online. For instance, a large-scale epidemiological research[12] synthesized data from reviews, meta-analyses and cohort studies to assess digital technology's correlation with depression and anxiety, and a robust analysis of these relationships in adolescents was conducted across multiple national datasets[13]. Both studies found only minimal evidence to suggest a causal or direct relationship between the amount of time that people spend online and mental health outcomes.

Such null findings on linear associations may partly be due to a U-shaped curve existing between Internet use and well-being. In fact, a further study within the US National Survey of Children's Health[14] found that moderate levels of digital screen time (1 to 2 hours per day) were associated with better psychosocial functioning among children than low (i.e., <1 hour) or high (~5 hours) levels.

While these large-scale studies are informative on a macro level, our ability to determine the nature of underpinning relations between Internet use and mental health from such research alone is limited. The last five years have seen an increase in studies attempting to provide causal evidence by assessing the effects of social media withdrawal on mental health. These studies hypothesized that, if such technologies are driving adverse psychological states from daily engagement, withdrawing oneself partially or entirely should produce notable changes in well-being.

Bringing together the latest evidence on this, a 2023 systematic review of 23 randomized controlled trials (RCTs)[15] indicated that partially or completely abstaining from social media use does appear to produce significant improvements across a range of mental health domains. Depression was the most frequently assessed outcome, with 7 out of 10 RCTs finding medium-to-large effects in favor of the social media withdrawal intervention. Three out of six RCTs assessing anxiety reported notable positive effects from withdrawal, while three out of eight RCTs assessing general well-being found only small indication of benefit. Some of the RCTs observed simultaneous benefits occurring across multiple domains, with an RCT of 111 adults reporting medium-to-large effects on depression, anxiety and well-being among those randomized to a week-long social media break, compared with controls[16].

On the other hand, a robust study of three preregistered field experiments (N=600) found that abstinence days from social media yielded no differences in well-being compared to using social media normally[17]. Furthermore, some studies have observed negative psychological effects from cutting down on social media. For example, one RCT of 78 students from the United Arab Emirates observed decreased life satisfaction and increased loneliness after a seven-day abstinence from social media compared with a control group[18], whilst another crossover trial in the UK found that daily withdrawal from social media decreased social connection, thus reducing well-being[19].

Overall, there has been a slew of null or contradictory findings emerging from both large-scale observational research[12-14] and RCTs[16-19] examining the "absolute" effects of social media engagement/withdrawal on mental health. Therefore, future research must move towards a more nuanced approach examining the factors and context which determine the psychological outcomes of social media engagement.

Our previous review[1] concluded by highlighting the need for further research to establish how individual characteristics, such as age, may influence the effects of Internet usage on mental health. Since then, the nuances of how age may affect the psychological impacts of Internet use have been deeply explored in a study[20] which analyzed the interaction between social media use, life satisfaction, and developmental stages in a large UK cohort including 84,011 individuals aged 10 to 80 years.

The findings revealed "windows of sensitivity" to the adverse psychological impacts of social media through the life course, with discernible differences between males and females in the developmental risks. Specifically, negative impacts from overuse of social media were first seen among females in the earliest stages of adolescence, between the ages of 11 and 13 years. In males, adverse relations between social media and life satisfaction appeared between 14 and 15 years of age, with both groups showing a further developmental sensitivity towards the end of adolescence (19 years)[20].

Along with age and gender, other studies have begun to observe that individual characteristics and situational factors can affect vulnerability to adverse outcomes of Internet use, typically finding that the same risk factors which increase marginalization and disadvantage "offline" (such as family dysfunction, mental health problems, disability, subjective feelings of loneliness and social isolation) also increase the vulnerability to online harms in young people[21-24].

From an academic perspective, these valuable findings serve to demonstrate that considering putative vulnerability factors within population-scale analyses can increase our understanding of how Internet usage impacts mental health. From a practical perspective, the windows of sensitivity and the key risk factors identified are immediately useful, in order to start exploring strategies to ameliorate adverse consequences of online time in those most at risk.

While recognizing the utility of such progress, the field can now move beyond it, by searching for the inter- and intra-individual factors underpinning people's "online lives", and how they determine the psychological, cognitive and social outcomes of Internet usage.

ENDLESS ENGAGEMENT IN THE ONLINE WORLD

The association between digital technology use and mental health is complex. On the one hand, it appears that some public concerns over general technology use and adverse outcomes in young people may be overblown, given the lack of robust evidence for overall effects[25]. That said, the Internet does inarguably provide a platform for young people to become exposed to "online harms", with many valid concerns expressed over obvious threats such as cyberbullying, exposure to pornographic material, and gambling[26-29]. Moreover, the gravity of the issue of exposure to suicide-related content has been highlighted by a study[30] reporting that almost a quarter of young people who died by suicide in a UK sample had suicide-related Internet experiences (e.g., searching for methods of suicide). Since these discrete threats from online world have been comprehensively examined elsewhere[22,31,32], we instead seek here to elucidate how the nuances of general Internet usage, apart from these high-risk activities, may affect cognitive and psychological outcomes.

The most problematic Internet usage is referred to as "Internet addiction". Instead of defining it by a quantifiable amount of time spent online, an addiction to the Internet is better conceptualized as a compulsive need to engage with specific online platforms (e.g., social media or gaming) at the expense or neglect of other personal, social and occupational responsibilities[33]. Key indicators of addiction include prominent shifts in mood when away from the Internet for even a relatively short while (withdrawal symptoms), an increasing amount of time spent on these platforms to achieve satisfaction (tolerance), and conflict with other activities and/or real world social relationships[33].

Despite the term "addiction" describing a relatively extreme usage that affects real-world social functioning, a recent meta-analysis across 32 countries involving 63 independent samples with >34,000 individuals[34] revealed that, even under the strictest classifications of addiction to social media, the general prevalence is estimated to be around 5%.

While many "normal" behaviors not involving the Internet have the potential to become addictive, an emerging body of qualitative research has begun to shed light on how the online world specifically seems to exert a strong compulsion towards constant usage in some young people[26,27,29,35-41]. Adolescents express concerns about a "*constant stream of entertainment*"[41], affecting critical activities such as homework and sleep[38,41]. Some young people connect their digital behaviors to addiction-like cravings. For instance, in a mixed methods study conducted in the US, focusing on university students' social media use, a participant elaborated: "*I created an unhealthy habit for myself that is like playing a slot machine. It leads to me craving to check social media more for the gratification*".

Some parents also directly witness the addictive potential and resultant distraction and unresponsiveness of their children[27,35]. For example, in an Australian qualitative study[27], parents reported that certain online games are so addictive for children that they can impact self-regulation and standard self-care behaviors to a dramatic extent, in even the youngest of digital media users: "*We had to ban Roblox for ages because he wouldn't go to the toilet. He would wet himself playing games because he didn't want to die in the game*".

The difficulty of self-regulation when engaging with social media is also depicted by the novel qualitative literature capturing the experiential aspects of this topic, with participants describing in detail the challenges towards cutting down their time on such platforms[42]. Several users describe how social media algorithms are designed to encourage prolonged, high-frequency usage[41]. Platforms such as Instagram may promote or exacerbate compulsive use through push notifications, algorithm-generated content recommendations, and continuous binge-watching functionalities such as auto scrolling[29,40]. Notifications, especially from social media and online messaging, are viewed as rewarding yet highly addictive, contributing to extended screen time from the perspectives of young people, parents and health professionals[36,40,43]. Despite attempts to turn off notifications[41], young adults describe feeling compelled to check them, and the act of checking becomes a habitual process[29], contributing to extended screen time[36].

Several of these engagement facilitators feature prominently in the aforementioned lawsuit from US states against Meta (Facebook), which suggests that the company used: a) dopamine-manipulating recommendation algorithms; b) social comparison features; c) audiovisual and haptic alerts that cause users to turn their attention away while at school and sleeping; d) visual filters that can promote body dysmorphia, in order to gain and sustain young people's engagement[10].

The psychological mechanisms behind this compulsion to check, and the difficulty to disconnect, are described as challenges to attention, self-control, and time management. For instance, the ability to successfully self-regulate engagement can be challenging when users are in a "*trance*" or "*mindlessly scrolling*"[42]. In an Australian qualitative study with university students, a young person reported: "*I need someone else to kind of tell me, to just catch me out on that, because once I'm on there and I'm scrolling,… I'm stuck*"[42].

In recognition of this, various self-regulation strategies have been reported by participants in qualitative studies, such as reducing accessibility by moving phones out of reach or hiding them, muting phones, disabling notifications, setting alarms, planning out the day, and keeping busy[41,42,44]. In some studies with adults, participants expressed a strong motivation to uphold digital discipline, but acknowledged the need for more severe restrictions, such as uninstalling apps, to achieve self-determined disconnection, especially during periods of emotional vulnerability[44].

FROM NURTURING CONNECTIONS TO "FEAR OF MISSING OUT"

As the science in this field is progressing, it is becoming clear that the Internet-brain relations are not only dependent on quantity of usage, or even individual characteristics such as age, gender or other factors which may affect vulnerability. A more fine-grain understanding of the impact of Internet usage on mental health can be gleaned by moving away from looking at outcomes on a linear spectrum of "good" to "bad". It should be acknowledged that users can be experiencing both positive and negative psychological effects of Internet usage simultaneously, through the multitude of ways by which their lives are entwined with the online world[45].

Studies have been using objective metrics to differentiate between types of social media activity, such as primary posting one's own content vs. commenting on or "liking" other people's posts, or "active use" (e.g., targeted one-on-one exchanges such as sending private messages or posting status updates) vs. "passive use" (e.g., monitoring the online life of other users' profiles)[46,47]. However, such research has so far failed to produce consistent evidence for a specific style of Internet engagement driving positive or negative mental health outcomes[46,47]. Instead, most of the evidence on how specific uses of the Internet can differentially affect mental health is found in research focusing on the experiential aspects of young people's engagement with digital devices. For instance, large scale surveys have found that, while over 90% of adolescents identify at least one way in which technology is negatively affecting their everyday lives[48], the majority also report that being online has positive effects on their work, education and social relationships [49].

Social media platforms provide opportunities for users to maintain and strengthen social connections, which can be especially beneficial in circumstances where physical interactions are limited, such as remote working, or for individuals with mobility issues[50]. In particular, there is research evidence that social media use contributes to the overall ability of older adults to engage more fully and effectively in social contexts, thereby enriching their social well-being and interactions[50]. Moreover, during the COVID-19 pandemic, several studies observed that social media usage ameliorated some of the social isolation produced by lockdowns in youth[51], while adolescents who did not have access to a computer experienced substantially worsened mental health outcomes over that period[52].

Using the Internet to stay connected to friends is a prime example of a behavior that can bring psychological benefits. However, the social aspects of the online world can also result in a "fear of missing out", a phenomenon referred to as "FOMO". FOMO is people's apprehension that they are missing rewarding experiences which others are having, resultantly creating a strong desire to stay continually connected, which has been linked with both increased social media use and poorer mental health outcomes[53].

A few RCTs have explored this experimentally. One trial of 61 adults observed lower rates of FOMO after a 7-day social media break compared to a control group[54], while another trial of 143 students found no differences in FOMO after participants were asked to limit their social media use to 10 min per day for 3 weeks compared to using social media as usual[55]. Indeed, it is even conceivable that withdrawing from social media could increase adverse emotions tied to FOMO in long-term users whose social lives are deeply connected with online happenings.

Again, the nuances of this phenomenon are best captured in qualitative research, which shows that motivation to engage and spend more time on social media is compounded through social and recognition needs, exacerbated by comments and "likes", which foster habitual and compulsive usage[39,41]. These themes are covered in a single quote of a female teenager reporting that: "*It's just so addictive. When you hear a notification it's really hard not to look at it, especially when it's a fun group chat with your friends and you don't want to miss out*"[36].

Herein lays the dual nature of Internet engagement. It serves as a beneficial tool for maintaining social relationships, but simultaneously fosters a sense of missing out when one is disconnected. This highlights the need for understanding and educating individuals on fostering a balanced sense of connection in the online world.

SOCIAL COMPARISONS AND SELF PERCEPTIONS IN THE ONLINE WORLD

The usage of Internet also leads to social comparisons, which is another key mechanism through which online lives can exert positive or negative effects on psychological well-being. For instance, a study of 150 students in Pakistan[56] presented compelling evidence that daily usage of Facebook decreases self-esteem, due to the high amount of young people (88%) engaging in social comparisons when using that platform. These results have been supported by a study in Germany, which administered self-report questionnaires every day for 2 weeks, finding that daily social media use resulted in lower self-worth, which was mediated by upward social comparisons[57].

On the other hand, two crossover trials measuring multiple facets of well-being, respectively in 600 and 236 participants[17,19], found no evidence to suggest improved self-esteem after social media abstinence compared to normal usage. Similarly, a larger, longer-term (3 weeks) experience sampling study from the Netherlands observed that the effects of social media on self-esteem varied substantially among individuals, with some of them even reporting positive effects[58], again speaking to the idea that the outcomes may be more linked to the specifics of *how* an individual uses and responds to these platforms.

Within the debate around the psychological effects of social comparisons in the online world, one aspect gaining considerable attention is the impact on body image, and the potential for unrealistic social comparisons in this domain to result in or perpetuate eating and weight disorders.

There are numerous features of Internet and social media that are thought to contribute to the onset and maintenance of eating, body image and weight disturbances. Users are often exposed to an abundance of content that depicts unrealistic body shapes and idealized eating and exercise plans[59]. Furthermore, social media platforms and photography apps also feature image editing tools, which results in proliferation of enhanced, edited or manipulated photographs of unattainable body types in the online world. This, alongside the use of physique-enhancing drugs by influencers while presenting themselves as "natural"[60], leads to a hyper-focus on physical appearance in the online world which is thought to increase preoccupations with eating, shape and weight[61]. Furthermore, there has been a proliferation of online groups promoting dangerous weight control behaviors, such as pro-eating disorder websites and forums, which can also adversely influence the eating and exercise patterns of vulnerable individuals, particularly young women[62].

A substantial amount of work has investigated the relationships of social media usage with eating, body image and weight disturbances, and meta-analytic research has provided evidence of cross-sectional, longitudinal and causal associations[63,64]. Nascent research is further investigating the psychological pathways by which social media usage confers risk to these issues. The available evidence suggests that "online social comparisons" may result in internalization of appearance ideals, and this, along with the perceived pressure to conform, is the mediating mechanism for Internet-induced issues with body image and eating[65,66].

Qualitative research also shows how such social comparisons can affect even those individuals who are aware of misleading presentations in the online world, influencing their body image and broader perceptions of their selves and lives. One user explained that "*a person has a feeling that they have a boring life or that everyone is beautiful and amazing because they see many profiles where the most beautiful things are presented, an abstract image of a person… So I think that influenced me even when I realized it… even when it was not a real image of life*"[67].

Much less has been done to understand whether the above risk relationship is also underpinned by an impairment of neurocognitive functions. Deficits in inhibitory control could be one explanatory mechanism linking social media use with eating, body image and weight disturbances[68-70]. In fact, neurocognitive research indicates that the activity of brain regions involved in this cognitive process (e.g., the mid-cingulate cortex) may be impaired in individuals who use social media excessively[71], similar to what has been reported in those displaying symptoms of food addiction and binge eating[68,72].

Attentional bias is another cognitive process that may be involved. Research using eye tracking technology and information processing tasks (e.g., dot-probe, Stroop task)[73,74] indicates that people with underweight eating disorders show selective attention to appearance promoting or threatening stimuli (e.g., attractive vs. unattractive photographs, images or words), which may be mediated by an overactivation of the amygdala and the ventromedial prefrontal cortex[75]. In contrast, people with obesity or binge-eating disorder display attentional biases towards food cues (i.e., words or images of hyper-palatable foods) using these same paradigms, which appear to activate the neural circuitry implicated in reward seeking, in turn inducing food craving and susceptibility to overeating[76]. Extrapolating these findings to the digital environment, it is plausible that, in some individuals, exposure to the ubiquitous online content geared towards appearance (e.g., selfies, muscular and slender physiques), exercise (e.g., motivational quotes) or food (e.g., fast food advertisements) contributes to the onset or persistence of certain eating, body image and weight disturbances via these attentional biases.

While this presents a clear risk for users who are engaging with social media in ways that accommodate their biases in a detrimental manner, it also provides an opportunity for addressing misperceptions around ideal and attainable body shapes in a positive manner. An example is given by an experiment[77] in which undergraduate females were exposed to a series of TikTok videos either promoting body neutrality or fitting with usual narratives around idealized physiques. Post-exposure assessments indicated that the neutrality group experienced heightened body satisfaction and improved mood, in contrast to peers who viewed typical videos.

These findings highlight that, if used correctly, social media may have a potential for improving body image perceptions in young people. More insights in this regard could be gained from further investigation into the cognitive mechanisms underlying social comparisons in the online world. This is particularly true with respect to attentional biases, as certain types of technology usage have been thought to alter attentional processes themselves, as discussed in the next section.

POINTLESS DISTRACTION VS. POSITIVE STIMULATION

In our previous review[1], we discussed the nascent evidence around the ways in which Internet use may affect our cognitive abilities across the life course, particularly with regard to the two areas of neurocognition which had received the most research interest at that time. First, how attentional capacities may be influenced by the continuous influx of digital content and notifications. Second, the leading hypotheses and evidence around how ubiquitous access to unlimited factual information online may affect our capabilities for storing and retrieving information ourselves. Since the time of that review, a wide body of literature has emerged in this area, offering further insights into the impact of online activities on attention, memory and other aspects of human cognition.

Recent large-scale observational studies indicate that extensive device use in children may indeed negatively impact their concentration. For instance, the relationship between screen time and attention based on parent-reported data was examined in over 2,300 preschool-aged children[78]. Results showed that children with more than two hours per day of screen time (13.7%) were almost six times more likely to present clinically significant inattention problems compared to children watching less than 30 min per day, along with showing increased incidence of clinically significant attention-deficit/hyperactivity symptoms.

Despite these strong associations, it remains difficult to directly attribute attentional difficulties in young people to Internet usage, given the lack of causal evidence for improving attention through withdrawal. For instance, an RCT of 76 students found that one week of being instructed to reduce social media by 50% led to no differences in behavioral or self-reported measures of sustained attention when compared to reducing social media by 10%. However, the mean reduction in social media use in the control arm was actually 38%, which may have explained the null findings[79].

Results from the latest neuroimaging research have provided a more comprehensive view of the interaction between digital device use and brain functioning. For example, the Adolescent Brain Cognitive Development (ABCD) study had gathered data from a total of 11,878 participants aged 9 to 10 years by the time of the latest analyses, performed in 2023[80]. The evaluation of changes in brain network dynamics over a two-year period found no consistent evidence for causal relations between digital screen media usage and functional connectivity in children.

Further insights on this are provided by another investigation[81], which delved into the specifics of how various types of screen media activities were related to brain structure and cognition among 4,277 children from the same ABCD study. Some screen media activities were found to be linked to poorer cognitive outcomes, while others were associated with better performance. For example, activities such as video watching and gaming appeared to hold links with structural patterns indicative of greater maturation in the visual system. Furthermore, gaming activities correlated with increased orbitofrontal volume, holding a positive relationship with fluid intelligence. On the other hand, results indicated a negative relationship between social media use and crystallized intelligence. Along with revealing the complexity of the relations between screen media activities and cognitive performance, these findings provide further evidence for the principle of moving beyond examinations of overall screen time metrics, to instead focus on delineating how the nature of people's interactions with the online world may determine cognitive as well as psychological impacts of digital device usage.

Beyond population-scale neuroscience research, several smaller-scale behavioral studies have provided a more fine-grain understanding of how digital devices affect attentional capabilities in the actual moment of usage. A momentary assessment protocol[82] was used to assess how university students' tendency to become distracted from important tasks (measured via self-reported procrastination) was related to their mobile smartphone use in real-time (captured by passive data collection). While only weak associations were found when looking for overall trends across the entire sample, the results presented compelling evidence for individual variability in the type of smartphone uses which encourage procrastination. Some users were more readily distracted by video streaming (e.g., YouTube), others more so by browsing the Internet, and others turned attention to online games when procrastinating[82]. Using a similar methodology, another study[83] also found no overall associations between how often adolescents check their phone and procrastination. Instead, the degree of task delay across individuals was related to how "automatically" (i.e., habitually) the participants used social media, rather than the frequency.

These behavioral observations are aligned with the recent qualitative literature, which shows how the habitual nature of social media engagement presents threats to attention. For example, in an Australian qualitative study, a student reported that "*[checking social media is] 100% an automatic thing. I would just like go to bed, lay down and just immediately go on my phone and start scrolling, and before I realise it, like four hours later, then I become conscious*"[42]. This captures the broader experiences of young people, who often voice concerns about the impact of smartphones on attention span and concentration, leading to struggles with distraction during unstructured time[39,43]. Within this, the phenomenon of getting lost in social media is often highlighted, with participants entering a "*trance*" or "*mindlessly scrolling*"[42], leading to a loss of track of time[39,42,84].

On the other hand, an emergent qualitative literature has highlighted that the cognitive outcomes of Internet usage depend on both the specific context and the individual. A central consideration is that digital devices provide children with endless opportunities for education[26,38]. For example, in a Canadian study exploring parents' perceptions of screen time in children, one participant commented: "*Not to say that iPads are really great, but my daughter does learn things from the iPad… she does puzzles, and has the memory game on there*"[26].

Alongside this, whereas media multitasking has traditionally been presented as an adverse behavior for cognition in children and adults[85], qualitative studies have revealed that Internet-enabled multitasking, such as listening to podcasts while commuting or completing chores, can also have positive effects[44,84], making individuals feel "*productive*", expanding their world while physically engaged in other tasks[84]. Interestingly, the tension between emotional gratifications of multitasking and its potential hindrance to deeper cognitive processing is also experienced by technology users. For instance, in a Norwegian study[44], the contextual aspects of how digital reading (and/or audiobooks) affects the processing of textual content were captured, with several participants indicating a preference for lighter texts when using digital screens, compared to preference for paper-based alternatives when reading deeper works, as "*serious reading needs paper*"[44].

Gaming is another area of screen time with mixed perceptions among parents and young people. While the heaviest gamers do experience more communication and academic problems at school[86], both parents and young people report benefits from moderate levels, such as developing visuospatial skills and improving cognitive functioning[87].

Collectively, these findings from neuroscience, behavioral and qualitative research suggest that a possible method for attenuating the detrimental cognitive effects of digital device use could be through providing individuals with new means for consciously identifying which aspects of their own online time are most likely to interfere with their tasks and goals. This could allow providing a more personalized intervention to deliberately address one's own habits than the general withdrawal protocols that fail to produce significant improvements in cognition[79].

THE OFFLINE EFFECTS OF AN ONLINE WORLD: IMPLICATIONS FOR BODY AND BRAIN

Another putative factor determining the cognitive outcomes of digital engagement is how time spent online may be impacting other "pro-cognitive" behaviors, such as physical activity and sleep. Despite the numerous advantages that the Internet offers, it has contributed to a notable rise in sedentary behavior across the population[88], which in turn could impact attention, memory and other cognitive aspects[89]. The strongest empirical evidence supporting this possibility, sometimes referred to as the "displacement hypothesis", is provided by various meta-analyses and reviews that have either specifically investigated the association between sedentary behavior and cognition[90-93], or examined the relationships between multiple lifestyle factors (including sedentary behavior) and cognitive outcomes[94,95]. The findings consistently indicate that higher levels of sedentary behavior are linked to reduced cognitive function and heightened risk of cognitive dysfunction across the lifespan[96].

Cognitive decline has been reported to be half as prevalent among adults who engage in sufficient physical activity, compared to their less active counterparts[97]. Engaging in physical activity at any point in adulthood, and to any extent, has been found to be associated with a higher cognitive state in later life[98]. This idea is substantiated by moderate-to-strong evidence indicating that physical activity has positive effects on cognitive functioning both in early and late stages of life and in specific populations characterized by cognitive deficits[99].

Engaging in excessive Internet use through becoming engrossed in sedentary activities such as online browsing, social media engagement and gaming, in ways which could displace physical activity time, may represent a pathway towards cognitive detriments of digital device usage[100]. Within this, it is important to consider that different types of sedentary behavior may differentially affect cognition. Specifically, recent studies have indicated that "mentally active" sedentary time (such as reading a book or even playing video games) may be preferential to "mentally passive" sedentary behavior (such as watching TV or online videos), with the former being provisionally associated with better cognitive outcomes and lower incident dementia risk[96].

Supporting this, a recent UK Biobank study – including more than 1,000 patients with bipolar disorder and almost 60,000 psychiatrically healthy controls – demonstrated that, in both groups, a global cognitive score was inversely associated with mentally passive sedentary behavior (TV watching) and positively associated with mentally active sedentary behavior (computer use). Age-related decrements in cognition were more evident in those who engaged in less mentally active sedentary behavior[101].

Another pathway through which online time may affect cognition is through the potential impact on sleep[102]. The growing trend of people, especially youth, to spend more time engaging in online activities on a daily basis can result in substantial consequences for their sleep habits, including reduced sleep duration, erratic sleep routines, and impaired sleep initiation and cessation times[103-106]. This can have a direct impact on cognitive functioning, as a lack of sleep can affect attention, memory and executive functions[107]. Moreover, disruptions in sleep caused by excessive online activities can lead to difficulties in concentrating, learning, and remembering information[108]. Supporting this, a recent study has shown that the usage of digital devices before bedtime in adolescents is associated with slower reaction time and reduced attention span on continuous performance tasks, particularly in morning hours[109].

Another issue of concern has been the "blue light", which is the portion of the visible light spectrum emitted by digital screens that has a particularly high energy level compared to other colors[110,111]. Exposure to this light, especially before bedtime, can interfere with the production of melatonin[112], disrupting the sleep-wake cycle and leading to fragmented and less restful sleep[110], which in turn may have a negative effect on cognitive functioning[113]. In this context, exposure to digital screens during leisure time has been related to lower sleep quality in adolescents[114]. Addressing this through "blue blocking", which can be achieved via physical (i.e., screen filters or glasses) or technological (apps for reducing blue light emission) means, may represent a possible route for attenuating screen-induced deficits in sleep[115].

Overall, mounting evidence suggests an inter-connectedness of sleep, sedentary behaviors (including Internet usage) and physical activity, which is inseparable from their relationship to cognitive health across the lifespan. This is reflected in recent initiatives to develop "24-hr movement guidelines" which include physical activity, screen time, and sleep duration across the entire day. Adhering to these guidelines has been linked with higher global cognition[116] and total cortical and subcortical grey matter volumes in children[117], along with reduced incidence of cognitive difficulties in adolescents[118]. Furthermore, in pre-schoolers, the reallocation from sedentary behavior to moderate-to-vigorous physical activity was positively associated with inhibitory control[119]. Despite the potential benefits, adherence to the physical activity, sedentary behavior and sleep guidelines is worryingly low worldwide, especially among children and adolescents[120].

From a time-use epidemiology and 24-hour continuum perspective, increased Internet time, as a sedentary behavior, can displace time available for other healthy behaviors (physical activity or sleep)[121]. Thus, adverse cognitive consequences of Internet usage could be partly attributable to a cascade of cognitive consequences from these physical effects. If this is true, then addressing health behaviors in Internet users could represent a feasible and effective method for improving cognition, especially in healthy older adults[122]. Indeed, a meta-analysis found evidence that web-based lifestyle programs can positively influence brain health outcomes, and potentially offer a protective effect from aging-related cognitive decline[123].

While we may have a friend in the enemy for improving cognition throughout Internet usage (especially for certain populations such as older adults)[10], it does seem reasonable, from a public health perspective, to recommend that Internet use should not significantly contribute to increased sedentary time and should not displace physical activity time or sleep duration. Additionally, further research should be conducted to inform policy recommendations around displacing mentally passive with more mentally active Internet usage, in order to potentially attenuate the cognitive downsides of the increased sedentary time incurred while engaging with the online world.

REVISITING SOCIAL OUTCOMES OF "ONLINE LIVES"

While a primary concern around online activity is that it may detract from real-world social activities[124] and potentially lead to social isolation[125,126], it is also the case that many of the most used and time-consuming online activities are in themselves "social", albeit in an online context[34,127].

Blurring of boundaries between social media and real-life experiences is now viewed as an integral part of many, particularly young people's, lives. In the qualitative literature, the social nature of multi-screening is emphasized, with individuals reporting watching alongside people connected digitally[28,36,43]. Live gaming and personal livestream shows were also seen in qualitative reports as particularly "social", since they allow to interact with others digitally through memes and chat[29]. Qualitative findings further highlight changing communication patterns and a shift in norms to multi-communicating, with individuals frequently resorting to messaging on smartphones even during face-to-face interactions with each other[28].

Recent studies have demonstrated that social media and online games are more than time-consuming entertainment, and serve a purpose beyond just staying in touch with friends in the absence of real-world contact. Rather, research increasingly demonstrates that these activities actively shape social cognitive processes themselves[128,129]. One example of this is how engagement in social media platforms requires interpreting and responding to a broad range of emotional cues and perspectives, which potentially may hone face-to-face empathy skills[130]. A longitudinal survey of Dutch adolescents showed that social media use held a relationship to improved cognitive and affective empathy[131]. However, negative behavioral aspects of social media have also been noted, with research participants reporting that people behave differently on these media, often resorting to use of their phone as a protective sanctuary in challenging face-to-face social situations[41].

The psychological implications of social media feedback are also increasingly explored. Internet users seem to recognize the challenge of resisting the pressure to "care too much" about social media validation, underscoring the psychological impact of the pursuit of "likes" and comments on platforms such as Instagram and Facebook[36,41]. Additionally, recent findings indicate that health professionals also identify the "likes" feature on platforms such as Instagram as a significant motivator for compulsive use[40], as these simple indicators of endorsement can fulfill users' social and recognition needs, acting as a form of positive reinforcement.

The social aspects of Internet use are further emphasized in qualitative research as driving digital behavior, particularly with regards to the role of online actions or even inactions as important social signals[36,41]. Participants describe how failure to engage with friends' social media posts through "likes" and comments could be misinterpreted, leading to concerns about unintentionally hurting someone. One young person in a Norwegian focus group explained: "*Yes, the pictures were nice, but you don't always have to comment on every single one. But still, you feel like you need to, because… otherwise it may be like: "Oh, she didn't comment on my picture!" It may be interpreted negatively*"[41]. Affirmations on social media are viewed as potentially detrimental to emotional health by young people, in that, if participants receive limited affirmation from peers, it can lead to negative emotions[36]. However, the nature of these social media interactions, often devoid of non-verbal cues, can also lead to misunderstandings or a superficial understanding of complex emotional states[132]. As such, further research on disentangling these relationships between social media activity and social cognition are now needed.

As individuals move more and more towards receiving information (such as global and local news, political opinions and sociological insights) from online outlets[133-135], it is also notable that the social connections held by people on social media are likely to shape the information to which they are exposed[134,136]. This can lead to social echo chambers and result in online social movements that transcend into the real world[137,138]. The Internet does provide an arena for diverse viewpoints, which can enhance decision-making skills. Yet, caution needs to be given to how the echo chambers and filter bubbles prevalent in online spaces can also potentially lead to polarized thinking and impaired social judgment[136,137,139].

Anyway, the extent to which information from online sources actually shapes individuals' judgment remains debated, due to the complexity of how behaviors actually spread in online social networks[140], and the ability for related emotions to also spread across social media[141-143]. More research exploring the fundamentals of how complex behaviors transmit between individuals in real-world networks would now be useful[144,145]. This is specifically of interest in terms of social decision-making.

Online multiplayer games appear to offer a different dynamic to social media activity in relation to social cognition[146]. Online gaming often involves collaborative problem-solving and strategy development[147], which has been suggested to potentially allow enhancing of user perspective-taking and collective decision-making skills[146]. However, these environments can also foster competitive and, at times, aggressive behaviors[148], and some recent research suggests that this may negatively impact empathy and prosocial behavior[149,150]. While this research area is currently of much importance[147], a recent systematic review found a very limited number of studies which suitably investigated social cognition (as assessed by neuropsychological tasks) in relation to gaming[146]. Further empirical research on this topic is certainly needed.

The relationship between online social activities and cognitive processes is currently the focus of various lines of research, yet it is important to recognize that real-world activity can significantly shape online social functioning and abilities as well[141,145,151-153]. This interaction creates a multi-dimensional "feedback loop" between offline activities and online social contexts. For instance, individuals with extensive experience in sports or outdoor activities often demonstrate superior spatial awareness and strategy planning in online gaming environments, translating their real-world skills into the virtual world. Alongside this, recent research within neuroscience has revealed that individuals who were raised in areas that were complex to navigate spatially were also better at navigating virtual worlds[154].

This interplay can be intentionally harnessed. For example, some professional e-sports players report using physical and mental training regimens, akin to traditional athletes, to improve their reaction time, endurance, and overall gaming prowess[153,155].

Overall, these examples clearly illustrate the ongoing feedbacks between the online and offline worlds. Future research delving into the extent of these interactions across various domains will be crucial, especially as our online lives continue to intertwine with and impact our offline realities. This exploration will be pivotal in understanding the full spectrum of how digital and physical experiences shape human behavior and cognition.

THE ADVENT OF "CULTUROMICS"

The ongoing digital revolution, with increased societal switching to Internet use, is offering new opportunities to study population level shifts in interests, opinions and behaviors manifesting in the online world. The vast, readily available and rapidly growing body of online digital data contains valuable information on human behavior, daily rhythms, attention, interests, attitudes, norms and values, with a high spatial and temporal resolution. These represent key research topics of the emerging field of "culturomics", which is focused on the study of human culture through the quantitative analysis of large bodies of digital data[156,157]. Culturomics is increasingly used in a wide range of scientific disciplines, especially within social sciences and humanities[158].

Some of the commonly studied digital materials include social media, search volumes from web search engines such as Google, pageviews from online encyclopaedias such as Wikipedia, image and video sharing platforms such as Instagram and YouTube, and online news platforms, with analytical methods ranging from natural language processing to machine learning[157]. These approaches have been used to provide insights into various issues relevant to mental health.

For example, the diurnal variation of depression-related health information seeking on the Internet has been analyzed in Finland[159]. The study showed that the interest in depression-related terms and help seeking had clear diurnal patterns, consistently peaking during the night-time, between 11 pm and 4 am. In a similar vein, a text analysis of millions of Twitter posts was used to assess diurnal and seasonal mood rhythms, and their differences among individuals (i.e., chronotypes), cultures, and across the globe[160]. It was found that positive affects (such as enthusiasm, delight and alertness) and negative affects (such as distress, fear and anger) tend to vary independently. The former peak in the morning, likely due to positive effects of sleep, as well as near midnight, while the latter peak during night-time. It was also observed that seasonal peaks in depression and anxiety in the Northern latitudes are mainly driven by diminished positive affects, triggered by the reduced day length.

It is important to note that the use of online digital data in research faces certain caveats and challenges, such as uneven global Internet coverage and access, language barriers and cultural differences, data sharing restrictions, temporal data availability and decay, property issues, and personal data protection[161]. Nonetheless, if properly used, these approaches promise to become major tools in the field of social sciences, psychology and psychiatry.

Culturomics is also beginning to provide new insights into how the Internet is affecting our attention at a societal level, beyond the individual cognitive effects. Online social interactions and consumption of information are both characterized by attention transience, a pattern of diminishing public attention towards particular issues and cultural products[162,163]. Attention decay represents a natural process driven by various psychological and cognitive factors such as limited attention span, selective attention, and attention saturation and fatigue[162-164]. It generates periodical issue-attention cycles, which represent an intrinsic and predictable process by which the public gains and loses interest in a particular issue over time[163,165].

The process of attention decay has been intensifying with the hyperproduction, dissemination and consumption of online information and content, which increasingly compete, saturate, overload and exhaust cognitively limited attention spans. For example, by modelling data from various online platforms such as digitized books and magazines (Google Books), movie ticket sales (Box Office Mojo), Internet search volumes (Google Trends), social media (Twitter), forums (Reddit) and encyclopaedias (Wikipedia), spanning periods from six to 100 years, an increasingly steeper rise and fall of public attention related to a particular issue over time was observed[162], with increasing frequency of attention shifts between issues. A similar study on public attention towards different environmental issues based on Internet search volumes indicated narrowing windows of public attention, with attention half-life being limited to few days or weeks[163]. This research area may be relevant to the mental health field, particularly as dissemination of information on mental health issues and anti-stigma campaigns are concerned.

THE FUTURE OF MENTAL HEALTH IN THE METAVERSE

As technological progress continues to penetrate our daily tasks and social lives, the integration of virtual reality (i.e., replacing a real-life environment with a simulated one), augmented reality (i.e., adding digital elements to a real-life environment), and artificial intelligence technologies in online platforms is poised to revolutionize our understanding and practice of social interaction [166-168].

Virtual and augmented reality technologies promise a new frontier in how we interact and engage with each other, by offering immersive experiences that closely simulate real-world interaction[166,167,169,170]. Indeed, recent studies are demonstrating that these technologies have the potential to significantly enhance social understanding and empathy, as they can create environments where individuals can experience and navigate complex social scenarios in a controlled, yet realistic manner[166,169,170].

This immersive approach offers a unique platform for training and enhancing social skills, allowing individuals to practice and develop empathy and social understanding in diverse settings. Nevertheless, it also has the potential to distract users from real-world social interactions and the benefits that they can bring, determining an even greater influence of the online world on individuals' social relationships and processes in concerning contexts (particularly through potential addiction to these technologies, which currently remains untested)[170-172].

The idea of further immersing our social interactions and daily lives into the online world through virtual reality has received considerable interest and investment, through the concept of "the metaverse". The metaverse can be described as an expansive virtual space, generated and accessed through a combination of virtual and augmented reality technologies, existing continuously on the Internet, and persisting regardless of user engagement[172,173]. The metaverse also offers a high degree of interactivity, in terms of both user-environment interactions and user-to-user connections.

Notable features of the metaverse include a fully functional digital economy, enabling the creation, purchase and sale of virtual goods (including those for use by individuals' virtual selves, or "avatars"), and significant user-generated content, with users having the capability to both create and modify elements of the metaverse space itself. For all of this, interoperability is a key goal, such that the metaverse could eventually support the exchange of assets, data and avatars across various platforms and providers.

As of now, the fully functional and integrated metaverse remains an aspirational concept, with current manifestations primarily accessible through individual virtual and augmented reality platforms. While persistent virtual worlds exhibiting certain characteristics of the metaverse already exist on these platforms, they are not yet interconnected and all-encompassing.

The implications of the metaverse extend beyond entertainment and gaming, being relevant to a variety of fields, such as finance, education, professional development, and social networking. For the mental health field, the metaverse offers innovative avenues for patient interaction, data collection, and the simulation of complex social settings, thus opening new frontiers for research, clinical and even community interventions[172,173]. However, the mental health impact of the metaverse is unclear at the moment, and indeed its future is currently in flux.

Despite the ambitious efforts towards metaverse adoption demonstrated through the Facebook's rebranding to Meta, the move of its social networking platform towards an immersive virtual world has yet to be embraced by users. Similarly, the adoption of Decentraland – one of the most well-funded metaverse products, with a valuation over 1 billion US dollars – remains remarkably low. Preliminary investigations report that it has only 38 daily users[174], and that only 9% of user-created worlds in the metaverse are ever visited by more than 50 unique people[175]. Nonetheless, these are only single, early examples of such offerings, and these virtual spaces are likely to expand, improve and interconnect after initial growing pains.

There is an expanding literature on the potential of the metaverse in medicine, including the mental health field. The speculation and hope are well embodied in the term "MEDverse", conceptualized as the entry of the metaverse into a medical context[173], or the MeTAI, a metaverse of medical technology and artificial intelligence[176]. It has been argued that the metaverse, and related virtual reality platforms, may offer customized exposure to specific situations (social or environmental) that can be used to deliver the next generation of exposure therapies. Such therapies have been proposed for mood disorders, anxiety/phobias, attention-deficit/hyperactivity disorder, eating disorders, post-traumatic stress disorder (PTSD), and schizophrenia[172,173,176,177].

This approach can take the form of "avatar therapy", which involves immersive virtual reality where patients can interact with digital avatars representing various aspects of their own personality, and/or other entities. For instance, in the treatment of anxiety disorders or PTSD, patients can practice interacting with avatars in controlled social situations, or gradually exposing their own avatars to fear-inducing scenarios in a safe, virtual environment[170,172,177]. Avatar therapy can also be used for fostering self-compassion, through patients interacting with avatars of themselves in various states, helping to develop a kinder self-perspective, as demonstrated in a recent pilot study in which 15 patients practiced delivering and receiving compassion from themselves in a virtual body[178]. A major benefit to such interventions is the controlled nature of the virtual interactions and environments, which provides a uniquely customizable therapeutic tool that can be adjusted to the specific needs, personality and progress of the patient[172].

Complexities of avatar therapy include the currently poorly understood "Proteus effect", whereby individuals' behaviors and attitudes seem to conform to their avatar's characteristics[179,180]. Meta-analyses have consistently demonstrated a small-to-medium effect on behaviors and attitudes as a result of this phenomenon[179]. While this can be intentionally harnessed to facilitate positive outcomes (i.e., through building avatars with characteristics that align with therapeutic goals), there remains a risk for the Proteus effect to inadvertently drive adverse outcomes in unexpected ways. For example, an avatar therapy for social anxiety could begin with immersing patients into a busy social environment, but without any direct or challenging social interactions with other avatars in the space. While this may serve as exposure therapy for the social anxiety, the lack of meaningful interactions with other characters could lead to the patient feeling ignored or overlooked, reinforcing feelings of insignificance or inadequacy in ways which translate to other social situations.

More recent research has demonstrated that the Proteus effect also appears to translate across different digital contexts, with a cross-sectional study of 345 e-sport athletes revealing that their digital personality in the e-sport world influenced the nature of their interactions with a digital health care system[180]. Further research is required to establish how attitudes and behaviors within virtual worlds spill over to real life settings, and a thorough understanding of human interactions with avatars' characteristics would be crucial in mental health care intervention design, to ensure that the Proteus effect supports rather than hinders therapeutic objectives.

Like other emerging technologies, the clinical potential of the metaverse will be impacted by its approach to user privacy, active moderation (safety), and transparency[177]. These concerns have already limited the mental health potential of social media, even when efforts and intentions were well intended, such as towards suicide prevention[181]. Also, as with other digital platforms, the concern that time spent on the metaverse could have a negative impact on mental health has been raised[182]. In a qualitative study from the UK[87], for example, parents held concerns about their children using virtual reality that included contact with strangers or violence, or that may be socially isolating. Parents reflected that they would continue to prefer real-world engagement and exercise. As one parent put it: "*I would see it [virtual reality] as inferior to physical activity in the real world*".

The role of artificial intelligence in shaping social cognition can be equally transformative[183]. Its ability to analyze vast amounts of data can provide deep insights into human behavior and social interactions and lead to more personalized and effective online social experiences, increasing the influence on social cognitive skills[183,184]. Recent advancements, particularly with the development of sophisticated large language models, have significantly expanded the scope and capabilities of relational agents (i.e., computational artifacts designed to build and maintain social-emotional relationships with their users).

Although the potential for relational agents to shape human social activity has long been acknowledged[185], the extent to which modern artificial intelligence systems can offer more nuanced and adaptive human-computer interactions, transforming the way in which we engage with and comprehend social dynamics[183], has been only recently realized. These advanced relational agents can now understand and respond to a wide range of human emotions and contexts, providing interactions that are more personalized, empathetic, and contextually relevant[183,186].

The sophistication of these models lies in their ability to analyze and process vast amounts of linguistic data, allowing them to mimic human conversation with remarkable accuracy[187]. This enables a deeper level of engagement and a more meaningful understanding of social cues and norms. Whether by offering support in mental health applications, or assisting in learning and development, or simply providing companionship, these relational agents are becoming increasingly able to address diverse individual needs and preferences[188-190].

In essence, the evolution of artificial intelligence has not only made these human-computer interactions more engaging and realistic, but has also paved the way for a future in which technology can seamlessly integrate into the social fabric, enhancing our ability to interact and understand each other in a digitally connected world. Still, issues of bias in these models and concern for stigma remain. A proactive approach to creating large language models and artificial intelligence programs that promote ideals of care versus promulgating today's biases is critical, especially as the current generation of programs have been trained by reading the Internet and social media websites. It is saddening, but not surprising, that stigma around schizophrenia already appears in images of this condition generated by artificial intelligence[191].

Emerging qualitative research with both patients and physicians emphasizes that there is no current consensus in people's views on artificial intelligence, with perceptions ranging from highly positive to entirely negative[192]. For example, physicians have reflected on the potential of artificial intelligence for reducing their workload and the overall burden on the health care system ("*But it will dramatically ease our workload, won't it? Considering that there is currently a shortage of personnel and increased workload, it would be a very good solution*"), whilst patients emphasize that humans remain critical for the relational aspects of care interactions ("*I think that humans can express emotions, empathy, help, and give hope for a better tomorrow better than any machine*")[192].

The combination of virtual/augmented reality with artificial intelligence opens further avenues for social training and therapy[166-170,189]. For instance, in therapeutic settings, virtual reality can create safe and controlled social situations[190,193,194], where artificial intelligence-driven analytics can offer real-time feedback and personalization, enhancing the effectiveness of interventions aimed at improving social skills in individuals with social cognitive deficits[194,195].

This intersection of technology and social cognition could not only enrich our online interactions, but also provide valuable tools for addressing and improving social functioning in individuals with various needs. As we continue to integrate these technologies into our lives, their potential to enhance our social understanding and interactions can grow exponentially, making them essential tools for both personal development and clinical practice. The future of social cognition, in this regard, seems not only technologically advanced but also more empathetic and inclusive. Yet, the current concerns surrounding online social activity are also magnified to the same extent as the benefits[171,181,186,192].

CONCLUSIONS

The evidence and insights gained from this review can considerably advance our understanding of the Internet's impact on our mental health, cognition and sociality, moving beyond general trends and dichotomous foci of the "online brain" to further investigate how the specificities of individuals' "online lives" determine the outcomes of Internet-brain interactions. Through synthesizing the ground-breaking quantitative and qualitative research from neuroscientific, behavioral and sociological research on this topic, we offer a refreshed perspective on how digital interaction influences mental states, both on a daily or momentary basis, and over the life course. Overall, the latest findings underscore the complexity of brain-Internet interactions, and how outcomes are dependent upon a multitude of sociodemographic, psychological and behavioral factors, crucially documenting that Internet usage is not a singular experience, but rather varies based on individual characteristics and contexts.

Within this, a shift emerges from the traditional research questions or interventions which approach the Internet (and its various uses) as either "good" or "bad", to instead detail the potential for simultaneous positive and negative psychological and cognitive impacts from most online activities. Accordingly, future research is encouraged to adopt a fine-grained approach towards examining how the specifics of individuals' online lives influence their mental health, self-perceptions, cognition, lifestyle and sociality, considering the myriad ways in which Internet use is woven into the fabric of daily life.

Alongside this, the emerging field of culturomics provides the means for using the Internet (and the associated data) to gain a more dynamic understanding of societal changes in habits, attitudes, abilities and even interactions with the offline world. Furthermore, the potential of technologies such as virtual reality, augmented reality, and artificial intelligence to further transform the ways in which we interact (online and offline) is clearly emerging, while the need for a continuing rigorous evaluation of the possible neuropsychosocial impacts of the new technologies has to be constantly taken into account, in order to inform the next era of digital engagement.

Overall, the findings of this review move us towards gaining a nuanced, individualized understanding of the Internet's influence on psychological, cognitive and social functioning. On the basis of this, we advocate for future research, guidelines and initiatives to consider cross-disciplinary findings from neuroscientific, behavioral and societal levels of research, in order to adopt an evidence-driven and multidimensional approach towards addressing the benefits and drawbacks of our interactions with the online world.

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DOI:10.1002/wps.21188

The lived experience of mental disorders in adolescents: a bottom-up review co-designed, co-conducted and co-written by experts by experience and academics

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We provide here the first bottom-up review of the lived experience of mental disorders in adolescents co-designed, co-conducted and co-written by experts by experience and academics. We screened first-person accounts within and outside the medical field, and discussed them in collaborative workshops involving numerous experts by experience – representing different genders, ethnic and cultural backgrounds, and continents – and their family members and carers. Subsequently, the material was enriched by phenomenologically informed perspectives and shared with all collaborators. The inner subjective experience of adolescents is described for mood disorders, psychotic disorders, attention-deficit/hyperactivity disorder, autism spectrum disorders, anxiety disorders, eating disorders, externalizing disorders, and self-harm behaviors. The recollection of individuals' past histories also indexes the prodromal (often transdiagnostic) features predating the psychiatric diagnosis. The experience of adolescents with mental disorders in the wider society is described with respect to their family, their school and peers, and the social and cultural context. Furthermore, their lived experience of mental health care is described with respect to receiving a diagnosis of mental disorder, accessing mental health support, receiving psychopharmacological treatment, receiving psychotherapy, experiencing peer support and mental health activism, and achieving recovery. These findings can impact clinical practice, research, and the whole society. We hope that this co-designed, co-conducted and co-written journey can help us maintain our commitment to protecting adolescents' fragile mental health, and can help them develop into a healthy, fulfilling and contributing adult life.

Key words: Adolescents, lived experience, first-person accounts, mood disorders, psychotic disorders, attention-deficit/hyperactivity disorder, autism spectrum disorders, anxiety disorders, eating disorders, externalizing disorders, self-harm behaviors, mental health care, recovery

(World Psychiatry 2024;23:191–208)

Recent meta-epidemiologic findings indicate that the onset of the first mental disorder occurs before the age of 14 in one-third, before the age of 18 in almost half, and before the age of 25 in about two-thirds of individuals, with a peak age at onset of 14.5 years across all mental disorders[1]. Most adult mental disorders originate during adolescence (i.e., between 10 and 19 years of age[2]), when rapid growth and development take place in the brain[3]. The incidence of mental health problems in adolescents is reported to be increasing worldwide[e.g.,4].

Early onset is a main driver of the high personal burden of most mental disorders, compounded by frequent comorbidities[5,6], and reflecting a complex etiopathological interplay of genetic and environmental factors[7,8]. A related driver is the global crisis of the mental health care system[9], which is typically split around the age of 18[10] (children and adolescent vs. adult mental health care), leading to a lack of continuity of care.

These drivers lead to suboptimal outcomes[11], and contribute to the decreased life expectancy (up to 10-15 years) associated with several mental disorders[12-16]. The above picture has been magnified through the lens of the COVID-19 pandemic, which has substantially disrupted young people's mental health[17-20].

Despite their large and long-lasting effects throughout life, the mental health problems of adolescents are typically neglected. In particular, the subjective nature of their experience of mental disorders has been usually siloed in academic investigations lacking first-person perspectives or in autobiographical accounts lacking in-depth analysis.

To fill this gap, we conducted the first bottom-up review of evidence on the lived experience of mental disorders in adolescents. The study was co-designed, co-conducted and co-written by junior experts by experience – representing different genders, ethnic and cultural backgrounds, and continents – and academics, refining an earlier method developed by our group to investigate the lived experience of psychosis and depression[21-23].

We established a collaborative core team of experts by experience (patients, their family members and carers) and academics to develop the study protocol. The study was then co-conducted by these partners across the subsequent stages. We performed a comprehensive systematic search of Web of Science, PubMed and EBSCO, from inception until May 1, 2023. The search terms were (adolesc* OR youth) AND (qualitative OR "focus group" OR "grounded theory" OR "content analysis" OR etnograph* OR phenomenol* OR "lived experience") AND ("mental health" OR "mental disorder*" OR "mental illness" OR "behavioral disorder" OR "behavioural disorder").

We included qualitative studies providing first-person accounts that involved adolescents (range: 10-19 years of age[2]) with a current ICD or DSM diagnosis of a mood, psychotic, neurodevelopmental, anxiety, eating or externalizing disorder. We did not include intellectual disability, because of the language and expressive difficulties that characterize this condition. We added an extra category of self-harm behaviors.

Studies investigating people grouped on the basis of symptoms, experiences or other self-reported features, rather than a diagnosis, were not included. However, the retrieved papers frequently contained the recollection of individuals' past histories, thus indexing the prodromal (often transdiagnostic) features predating a formal psychiatric diagnosis[24].

All included articles were uploaded on NVivo, a qualitative data analysis software[25]. Independent researchers performed a thematic synthesis of selected sources based on line-by-line coding of the text in the Results/Findings sections of the articles, and generation of a preliminary list of descriptive themes and sub-themes of the lived experience of mental disorders in adolescents. Further sources – such as websites, blogs, or social media material written by experts by experience – were consulted at this stage, and relevant items were included.

The material was then shared across the collaborative core team and preliminarily classified across three overarching descriptive sections: "The inner subjective experience of mental disorders in adolescents", "The lived experience of adolescents with mental disorders in the wider society", and "The lived experience of adolescents with mental disorders in receiving mental health care". Each section comprised several themes and sub-themes. Some themes were further enriched by incorporating the parents' and carers' perspectives, as applicable.

In a subsequent step, we promoted a collaborative and iterative sharing and analysis of the preliminary experiential themes and sub-themes in three workshops. These involved a wide group of experts by experience from the Global Mental Health Peer Network (https://www.gmhpn.org), representing the lived experience of youth from over 40 countries; the children and adolescents' Mental Health Advisory Group (https://www.kcl.ac.uk/research/ypmhag), representing the perspective of youth in the UK; and the Outreach and Support in South London (OASIS) clinical service (https://www.meandmymind.nhs.uk)[26], representing the perspective of adolescents with emerging mental disorders. Overall, we involved 18 young experts by experience of variable gender, age and ethnicity from three continents, encompassing Europe (UK), Asia (India) and Africa (Botswana, Kenya, Zambia and Zimbabwe).

In a final step, the selection of experiential themes and sub-themes was enriched by phenomenologically informed perspectives[27-43] drawn on the included articles, workshops and academic expertise. Academics were also of variable age, gender and ethnic background, as well as from various continents (Europe, North America, South America, Asia and Oceania). The broader group of experts by experience and academics collectively interacted to draft and review the manuscript via a shared Google Drive platform. All experts by experience actively participating in the manuscript elaboration were invited to be co-authors. Experts by experience were offered reimbursement for their time adhering to available guidelines for participatory research[44].

In line with our previous publications[21-23], the words written or spoken by experts by experience are reproduced verbatim in italics. Commentaries from participants in our collaborative workshops are anonymized as personal communications. As previously indicated[21-23], this study outlines the most paradigmatic ways by which mental disorders express themselves across the majority of experts by experience on a global scale. However, we neither assume that the reported experiences are exhaustive nor that they are systematically applicable to all young individuals or their parents and carers. On the contrary, we frequently address in this paper the high phenomenological heterogeneity of the lived experience of mental disorders in adolescents.

THE INNER SUBJECTIVE EXPERIENCE OF MENTAL DISORDERS IN ADOLESCENTS

This section explores the inner subjective experience of mental disorders in adolescents. Different sub-sections focus on mood disorders, psychotic disorders, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders, anxiety disorders, eating disorders, externalizing disorders, and self-harm behaviors.

The inner subjective experience of mood disorders

Experiencing a change in one's personal identity

Adolescents undergoing a depressive episode often describe a change in their experience of self, that they have difficulties to explain: *"Like you don't feel yourself"*[46]. This feeling ranges from a loss of confidence to a persistent and negative sense of lost identity[46-49].

The comparison between how they used to be and their current experience is extremely painful, affecting all areas of life, particularly their relationship with schoolmates and friends: *"I used to be a really good friend, and now I'm not"*[47]. Some of them feel that the good aspects of their identity have been replaced by unpleasant ones: *"There is something wrong with me"*[47].

The weakened perception of the self may lead to a feeling of imminent personal failure: *"I'm going to fail in everything"*[47]. A sense of estrangement may be reported: *"My depression is like being a different person… it's like it's part of my personality, but it's overshadowing who I am"*[47].

The manic episodes are instead marked by an experience of consolidation of personal identity and possibilities: *"I felt like I could do everything, that I would still be the best at whatever I decided to do" (personal communication)*.

Experiencing overwhelmingly intense emotions

Adolescents often experience mood episodes as a chaos of intense emotions. During the depressive phases, they report feelings of mental pain and anger (*"I find dark elements in my life: sadness, anger, desperation and pain"*[50]), which may be so intense that they feel like drowning: *"With the depression spiral, you just keep going down and down"*[49]. Sadness is described as being *"to the deepest summit"*[51], often becoming an inconsolable *"cry for no reason"*[47].

During the manic phases, the intensification of all emotions is often perceived as confusing: *"I had so many thoughts and so many emotions in my mind; they all mixed together" (personal communication)*. Anger not rarely predominates over euphoria and enthusiasm: "*My immense rage increased at the same time as my desire to break everything, to feel things fall*"[52]. Anger and irritability may be experienced as an overflowing river "*that has always been present*"[53].

As adolescents have not typically developed mature coping strategies to contain their overwhelming irritability, they may resort to verbal or physical aggression towards themselves or others (*"I feel really angry, it's just like little things that get me irritable… I'll literally go mad… It's like I shout at them or punch things or just say stuff I don't even like really mean"*[47]) or bullying behaviors ("*I was turning into a bully but didn't want to turn into a bully*"[47]).

In severe depression, rather than experiencing an intensification of their emotions, adolescents may experience a profound numbness and inability to feel any emotion at all: *"I didn't really feel anything, like there was no happiness or excitement, but there was also no sadness. It was just like everything was grey"*[46].

Feeling trapped in their own minds

Adolescents in a depressive episode often describe feeling trapped: *"It is a disease that's like a black hole. It is hard to get out of it, and everything around us is dark"*[54]. They may also report feeling "*flooded*" by recurrent negative thoughts, self-doubts and ongoing ruminations: *"I'm thinking about more and more things, so it's like piling on top, so, the mood just kind of keeps going down"*[55].

During a manic episode, there may be an experience of unprecedented availability of the surrounding world, as if everything is easily achievable and within reach: "*The world was my playground" (personal communication)*. However, the sense of omnipotence is frequently chaotic and accompanied by racing thoughts and impulses: "*You can tell that you were jumping from one thing to the next and not concluding sentences and things like that*"[56].

Therefore, adolescents may eventually experience a painful sense of being trapped in their minds during both depressive and manic episodes. This feeling is amplified by an abnormal perception of the subjective time, which is stagnant in depression (*"It feels like life goes on a loop every day, everything feels tired, nothing feels fresh anymore"*[54]), and accelerated in mania ("*It was as if everything couldn't stop running", personal communication)*.

Seeing the surrounding world fading away

During depressive episodes, adolescents may experience their surrounding world as fading away: *"I'm separated from everyone else"*[47]. They usually do not share the entertainment of their peers, and this makes them feel alone and isolated: *"Everything is just harder to get through, and you want to isolate yourself"*[49]. Isolation may become an unpleasant necessity: *"'I forget that everyone else exists… I'm invisible and I like that' "*[47].

The sense of isolation from the surrounding world may also be related to an altered perception of the lived body, which is characterized by heaviness, tiredness, and lack of energy: *"I was always really tired, and I had no energy to do anything"*[47].

During manic episodes, adolescents may report greater ease in social interaction ("*I had always been shy but now I wasn't anymore", personal communication*). However, this sense of being more in tune with the surrounding world is only apparent and transitory[31]. They are not able to pause and stop to properly meet their schoolmates and friends, because thoughts and body are in continuous excessive movement.

Therefore, both in depression and mania, adolescents may ultimately experience the surrounding world fading away. Everything turns into a pointless and hopeless stagnation of personal purpose ("*What is the point anymore? There is no point!"*[48]) and boredom (*"Just try and do a lot of different things, think I was interested in them then get bored, and just get into a cycle of boredom"*[46]), or into a senseless race without a goal ("*I felt like I was in a video game", personal communication*).

The inner subjective experience of psychotic disorders

Experiencing a pervasive change in the lived world and self

Adolescents who experience psychosis for the first time often describe a pervasive change in their lived world and self. They typically struggle to understand the world distorted by the psychotic symptoms. The surrounding environment loses its familiarity and becomes a sinister place, full of unknown threats, whose signs must be reinterpreted[28,39,57]: *"I knew something was wrong"*[56]. Unusual perceptions (*"I shared space with faint voices and a grim loss of reality"*[52]), frank hallucinations (*"I started seeing and hearing stuff, having some unusual smells"*[58]) or delusions (*"I've got feelings that people are trying to plot against me"*[57]) emerge. The pervasive change in the lived world is insidious and mirrored in a profound change in the self that is difficult to explain.

During the first episode of psychosis, adolescents may feel that the world they inhabit is very different from that of their peers: *"Psychosis to me is just being absolutely drowned off the planet, like floating in space sort of thing, with no idea what is going on"*[59]. Because of the altered perception of reality, they feel that they cannot trust their mind as they did before: *"it is like a friend who betrayed you once, and you don't know if you can ever trust them again" (personal communication).*

Feeling like a fish out of water

Because of the experiences described above, adolescents with psychosis may feel extremely uncomfortable with others, *"like a fish out of water" (personal communication)*. They may describe a sense of radical fear and loss of familiarity when entering social contacts, and a significant detachment from self and the world: *"I was mentally disturbed, confused and not well, my mind was not my own"*[60]. These feelings are amplified by their painful awareness of being different from their peers and being addressed as weird, triggering persecutory interpretations: *"People are looking at me like I'm different"*[61].

The fear of social interactions and the feeling of being different from peers can often originate in childhood: *"I didn't really have any close friends"*[62]*; "I want friends, but I don't know how to make them"*[63]. In early-onset psychosis, the sense of being different is particularly marked, and may be reinforced in a vicious circle by the decline of school performance: *"In the first grade, I was in the top reading group… by the third grade I was in the bottom reading group"*[63]. These negative experiences may lead the individual to abandon school: *"I hated going to school and made up many excuses to stay home"*[64].

In other cases, this sense of being different from others can intensify and trigger an abnormal perception that the world is centred on the individual *("If I'm in crowds of people, especially if I don't know them, I'll sort of feel like people could be talking about me, people might be about to come up to me"*[57]*)*, or prompt delusional fears (*"I felt unsafe. I felt like someone was going to kill me"*[60]*)*. Adolescents may prefer not to share these feelings with others because they fear rejection: *"Don't bother trying to explain to my family or friends, I just keep it to myself… they're gonna think you're going mad"*[61].

A common related experience is perceived stigma (*"If I told someone that I have a risk of developing psychosis and perceive strange things, he would be disturbed and treat me differently"*[65]), exacerbating social withdrawal and isolation (*"After I got back from the hospital, I really couldn't get along with anyone… I like to play by myself best. I make up stories and fantasies"*[63]*)*.

The inner subjective experience of attention-deficit/hyperactivity disorder

Perceiving one's neurodiversity

Adolescents with ADHD may perceive it as a part of their personality present from birth[66-68]: *"Some people mistakenly see it as a condition or a disease or something. It's rather* a *trait that makes people neurologically different"*[69]. It may be felt as a constitutive element ("*If I didn't have ADHD, I don't think I'd be me*"[67]), or as a complementary but separate part ("*Part of me is because of my ADHD, that I'm the way I am, but other than that I definitely have my own personality*"[70]).

Some of these adolescents do not experience their neurodiversity as an impairing condition ("*I just lead a normal life*"[67]), identifying benefits such as having more energy, less need for sleep, and being more outgoing in social situations *("We are always the life of the party… we're cool; we know how to have fun"*[71]).

However, others may perceive their neurodiversity as a parallel dysfunctional version of themselves, which is difficult to integrate and accept (*"I get angry because my ADHD starts to kick in. If it's a really bad day, you see the angry [side] of me"*[66]), leading to "*outbursts of anger sometimes"*[66]. Some adolescents may rather conceptualize ADHD as a disorder that occurred to them[66-68], particularly when they notice the significant improvements associated with medical treatment: *"[Tablets] make me a bit good"*[66].

Feeling a lack of control

Adolescents may experience ADHD as a fluctuating condition [66,67], whereby subtle environmental triggers amplify a feeling of lack of control, and impaired concentration and attention[66]: "*When I am forced to stay still… it gives a build-up in my stomach, and it almost makes me feel like screaming*"[72]. More frequently, their experience of the disorder is completely unpredictable, and they report being "*on a roller coaster*"[72]. Consequently, they frequently experience a lack of control over "*the way [their] brain works*"[67].

Some adolescents may be aware of their inability to control their disorder. Consequently they strongly feel that their dysfunctional behaviors are "*not actually [their] fault*"[66,68], regretting other people's judgement that their behavior is deliberately planned[72]. Given this lack of control and difficulty in communicating it to others, adolescents may actually perceive the ADHD label as *"an easier way to explain*" their condition to other people[70].

The lack of control may also generate the feeling of being left behind: "*I wish people understood, I'm not stupid… I'm not as fast as you*"[72]. Moreover, a typical experience in adolescents with ADHD is the need for ongoing help in controlling, organizing and planning their own lives and *"keeping things together"*[71].

The inner subjective experience of autism spectrum disorders

Feeling neurodivergent in a puzzling world

Adolescents with autism spectrum disorders typically feel very different from their peers: "*It is like… American people write back and forth, and Chinese [people] write up and down*"[73]. Sometimes they explain their neurodiversity in terms of a biological condition: "*Just the paths of how things transmit in a neuro-typical brain and an autistic brain*"[73]. In other cases, they may need to label their condition to understand it fully: *"I'd rather be different and have a reason for it than not be different"*[74].

However, profound interindividual differences exist[75]. Some of them do not accept their neurodiversity ("*I hate myself who cannot do well like others*"[76]); others eventually accept it and would not like to change "*because it's the reason why I am who I am*"[74], and they "*like being different*"[74] or are even "*proud*" of it[75].

Neurodiversity makes the lived world of adolescents with autistic spectrum disorders an extremely challenging place, particularly when confronted with the neurotypical world ("*This world is still a puzzle to me, like how people act and how rules are*"[73]; "*I'm working my brain harder than anyone else*"[76]). They may feel their mind "*moving into chaos, like a messy office*"[77].

Their inability to understand the surrounding world may also lead to pessimism and depression: "*[Autism] can cause problems in your life that you may never be able to fix*"[78], where *"the negatives outweigh the positives"*[78]. Their puzzlement may be amplified by their sensory alterations, which can alter even positive perceptions of the surrounding world ("*[The sunshine] is too bright. When the weather is fine, it's painful for me; it's like I can't stand it anymore*"[76]), and trigger vicious circles of feeling uncomfortable and detached from reality *("If a baby really upsets me via crying I will go outside and I will start noticing that my clothes are annoying me. So, I will start itching and scratching, and it gets really annoying. And then I'll start sweating, and then that annoys me. And it just all triggers everything*"[77]).

For this reason, they rather enjoy the calming effect of predictable routines ("*Everything is just structured, just normal*"[77]) and minimal changes ("*I just don't like rushing… I live life at my own pace*"[77]).

Longing for human warmth and connections

Several adolescents with autism feel that "*loneliness in itself isn't great*"[73]. Rather, they long for few and warm connections: "*I do prefer having fewer people in my environment… I'd rather have a few close friends rather than just more friends*"[73]. Nevertheless, social relationships are simultaneously experienced as overwhelming: "*After a while, I find people a bit draining*"[75], because of difficulties reading, interpreting and understanding others' emotions[75]. It may be easier for them to interact with peers similarly affected by autism: "*They all have… their special way of fitting into reality, just like me*"[77].

In general, they worry about losing social relationships, "*messing things up with people*"[77], experiencing rejection and stigma, and feeling "*humiliated or embarrassed*" in social situations[77]. These experiences are particularly pronounced when they are required to show some emotional closeness or support, which they are unable to deliver: "*If someone is really upset… and they're asking me to help make them stop crying and I don't know how and… I'll just say, I'm sorry, I can't, and then I have to walk away, and of course I feel terrible*"[77].

The inner subjective experience of anxiety disorders

Experiencing the tsunami of an anxious body

Anxiety is described by several adolescents as an experience of physical oppression, of drowning in intense bodily emotions. Among the various metaphors used, some emphasize the bodily feeling of carrying a burden, such as having *"a heavy backpack"*[79] or *"a black sludge"*[79]. Others instead describe an experience of suffocation (*"You know how like you're underwater and your lungs start to get tight"*[79]; *"You can't breathe properly"*[81]), or physical pain (*"Anxiety hurts; well, for me it hurts physically"*[80]).

They typically perceive anxiety as *"an uncontrollable force"*[82], "*a big scary monster*"[83], or *"a malevolent tsunami that has engulfed my soul"*[82]. They may find themselves at the mercy of these intense and overwhelming bodily emotions, with no way out: *"You feel like you can't get out"*[81]. During episodes of intense acute anxiety (e.g., panic attacks), the experience of suffocation is often accompanied by an imminent need to escape the situation: *"The only thing that you're trying to think is you have to get out of here, you have to run… you have to go somewhere else"*[81].

Overall, adolescents with anxiety disorders typically feel stuck in their bodies: *"Everyone else's life is like fleeting by, and you're just sort of stuck in your own body"*[82].

Losing control of the anxious mind

Adolescents with anxiety disorders often experience a lack of control of their minds, sometimes described as a sense of inner conflict: *"It feels like a war against yourself"*[83]. For example, in cases of generalized anxiety, anything can produce an intense worry, and making decisions becomes an insurmountable nightmare[79], leading to a sense of not being able to live as anyone else: "*You kind of feel like you're not living the way that everyone around you is*"[83].

In the case of a panic attack, adolescents may describe the perception of subtle or sharp bodily sensations that set off an alarm in their mind (*"Your mind goes into like… the sirens on an ambulance… it goes into an emergency and it's thinking well there's a danger"*[81]) and then spread to the whole body (*"It normally starts in your fingertips and your toes go all really tingly and then like it just starts spreading up your legs"*[81]).

Living in a shrinking and unpredictable box

Adolescents living with anxiety disorders may also dread the world as a shrinking and unpredictable box. They typically describe a general sense of claustrophobia and the feeling of being surrounded by worries: *"It is like living in a box, and the box keeps on going smaller and smaller every single day"*[79].

Because of the sudden nature of their anxious states, they live on constant alert, unable to predict when anxiety will take over. Consequently, they may feel different from their peers (*"like a bit of a weirdo"*[82]), and are convinced that others cannot understand their experience (*"Obviously they won't understand"*[81]). At the same time, the attention of others may amplify their feelings of shame: *"It just brings attention to you, and you don't want attention"*[81].

For this reason, adolescents often hide their anxiety symptoms from others. Failure to do so may further increase their lack of control: *"While you're trying to manage a panic attack, you're also trying to look like you're not having one because you don't want people's judgement, and even afterwards you're embarrassed because everyone just saw you freak out"*[81].

The inner subjective experience of eating disorders

Controlling food to control oneself

Adolescents with eating disorders often report feeling overwhelmed by intense and disturbing emotions that they struggle to control. This experience encompasses many aspects of their lives: *"I feel that different areas of my life are out of control, and I'm not happy about other areas of my life, and so I look for another way to feel in control, to feel happiness"*[84]. They typically control their food intake and weight as a means to regain a sense of agency over their lives (*"One way you can guarantee control is through food, through weight, through exercise"*[84]) and to silence their inner feelings (*"When I experience a violent and uncontrollable whirlpool of fear and anger, I open the fridge and consume everything I find… the feeling of my stomach bursting brings a sense of relaxation", personal communication)*.

Their dysfunctional control of food is needed to avoid unknown or overwhelming feelings, bringing a sense of security in their lives: *"This is safe because it's familiar, I know how I feel, there are no emotions I don't know"*[85]. However, controlling food often isolates adolescents from the rest of the lived world, triggering feelings of detachment from reality: *"You feel like you're not in the loop… yeah you feel like you're missing out… coz life's going on without you"*[86].

Desperately searching for an idealized identity

Adolescents with eating disorders often strive for an idealized image of themselves, originating from deep feelings of inadequacy. Even small details are scrutinized as they strive for an unattainable and unrealistic ideal and desperately attempt to recover their identity: *"I wish I had her body"*; *"Look at her legs, I wish mine were like that" (personal communication)*. Their sense of inadequacy is intensely expressed through a constant search for recognition and a need to define themselves as if their identity composition was a never-ending task.

This experience is so pervasive that they can even identify themselves with their eating disorder to be somebody or to establish a sense of identity: *"At first, I was completely taken over by the eating disorder because I was unaware of it"*[87]. In other cases, their disorder can be perceived as an external or inauthentic aspect of their identity, "personified" as an inner "voice": *"If I'm eating, it's like [hearing a voice saying]: 'should you really be doing that?' and 'don't do that, you're going to have to make yourself sick' "*[85].

The relation between the self and the eating disorder changes dynamically over time: *"It's an inauthentic part because it's not me… but over time, it has gotten more closely connected to me"*[87].

The inner subjective experience of externalizing disorders

Feeling like a bottle full of rage

Adolescents with externalizing disorders typically experience very intense anger, which they are not able to understand, and which overtakes any other emotions: *"When I'm getting angry… it all happens fast… I was very much out of control. I got angry very quickly and very badly"*[88]. Their outbursts and lack of control dominate their lives, to the point that they are frightened of their own behavior: *"I go mad. I've scared myself. My emotional state is wonky"*[88].

This lack of self-regulation is frequently experienced as an impulsive behavior, hindering their ability to consider negative consequences: "*I'm always quick to take actions without considering the consequences"*[89].

Adolescents with externalizing disorders may struggle to tolerate frustration, further fuelling their anger: "*When things don't turn out my way, I do whatever I want"*[90]. They may also feel vulnerable to criticism and advice, leading to frequent arguments and confrontations: *"When my friend advised me not to do bad things, I did not listen to him, and then we started to argue"*[91].

Feeling misunderstood and rejected

Adolescents with externalizing disorders often feel misunderstood and pressured by adults. This amplifies their sense of frustration and intensifies their anger, which may be violently expressed in out-of-control acts: *"[My mother] is always saying terrible things and that everything is my fault… I don't like that. They have to understand that you have problems"*[92].

They often report poor relationships with their parents, who may consider them incapable, further triggering their outbursts: "*My father thinks I cannot do anything; when I wanted to repair a pot or lighter, he grabbed them and said give it to me you cannot do it, so I smashed them"*[91].

The absence of familial understanding is often perceived as an insurmountable rejection, fostering emotions that are too intense and complex to handle outside verbal or physical outbursts and deviant behaviors: "*I'm stressed. I sometimes don't go home but stay at my friend's place taking drugs just to ease the stress. I go through this at home because my parents are very strict and harsh to me"*[89].

The inner subjective experience of self-harm behaviors

Transforming psychic into physical pain to control it

Adolescents who manifest self-harm behaviors often describe an urge to make psychic pain more tolerable, turning it into physical pain: *"It takes my focus away from another kind of pain, like the pain inside, like the way I feel. So, it overtakes that, so I kind of forget about the other sort of pain"*[93]. This is associated with the impression of better controlling affective states and modulating them through physical pain[94].

In other cases, they feel the need to overcome an indefinite psychic numbness and to perceive pain to feel alive: *"I am doing it to feel pain, to remind myself that I can still feel pain because at the moment I feel nothing. I feel numb, and it's my only way that I am reminding myself that I am still here, that I am still alive, by seeing the blood"*[93].

Self-harm may be perceived as having a protective purpose against even more serious behaviors (*"I think it's a way of taking care of yourself, because I feel in a way like self-harm stops you thinking about suicide as well"*[93]) or as bringing order to uncontrollable mental chaos ("*Self-harm collects those feelings. Then many painful things happen, and you can't understand... you just feel so much at once, it's like a storm – it's much easier to collect it all in one physical pain"*[95]).

Therefore, self-harm behaviors may be accompanied by an intense sense of relief: *"My body knows; I have that craving, it's like it will not stop until like I hurt myself"*[93]; *"It would be a relief from basically everything that was going on; the stress"*[94].

Self-harm behaviors may also become one of the few stable experiences in the lives of adolescents, while everything else is constantly changing, and are therefore associated with the confidence of having something they can count on: *"I did it when I couldn't do anything else. It was something to rely on"*[95].

However, in other cases, self-harm may actually index a desire for self-punishment: *"I become sad and feel a pressure to harm myself. I must do it because I have been bad, in a way"*[95]; *"I say it to myself, that I am a disappointment and need to be punished for that, so 'for this mistake you need to be punished' and I accept that"*[96].

Shouting for help without words

Self-harming behaviors may also represent an implicit cry for help in the context of expressive and communication difficulties: *"When I did it for attention, it was because I did not know how else to get help"*[97]. These behaviors are aimed at securing support: *"People should be interested in what's behind self-harm. I use self-harm to get someone worried"*[95].

However, self-harm is often conducted in secret due to fears of rejection or negative judgement from others: *"People who self-harm often go to great lengths to hide the damage. It's personal, and they don't want to be judged for it"*[97]. As such, several adolescents who self-harm do not accept the idea that it may represent an "attention-seeking" strategy, reiterating the authentic nature of their mental suffering: *"People who self-harm are expressing deep pain! The pain is real!"*[97].

THE LIVED EXPERIENCE OF ADOLESCENTS WITH MENTAL DISORDERS IN THE WIDER SOCIETY

This section explores the lived experience of adolescents with a mental disorder in the wider society, looking at three overarching narrative themes of this interpersonal dimension: a) the experience in the family, b) the experience in the school and among peers, and c) the experience in the social and cultural context. For a) and c), we also cover the parents' perspective.

The experience in the family

Suffering a painful lack of understanding

The subjective suffering of adolescents is enhanced by the parents' lack of understanding or acknowledgement of their mental disorder[98,99]: *"The first thing they [the parents] felt was like 'this is not a real illness', 'you should not be telling us about this'... I felt I was being put under the rug" (personal communication)*. They may not feel accepted for who they are with the existing disorder, struggling to meet their parent's expectations: *"My dad says things like 'I didn't raise you to be sad, I raised you to be strong because this is something from a weak person' "*[51]. Sometimes they need to resort to drastic measures to convince their parents to recognize and accept their mental suffering: "*I literally had to take myself to a mental hospital for my mother to listen" (personal communication)*.

As the identity of adolescents is particularly fragile, the full recognition of their mental disorder and associated needs by their immediate caretaker is essential[36,42,100]: "*I guess it would be nice if they'd console me, but all they said was 'take it easy'"*[101]. Downplaying the severity of the mental disorder does not help adolescents make sense of their suffering, adding to their confusion and desperation: *"I cried, and I told my mum that I'm not feeling well and I want to go and see a psychologist. And then she said that I don't have to worry and that I'm not depressed"*[102]. This amplifies inner perceptions of loneliness, embarrassment and shame: *"I did tell my parents that I was hearing voices, and they kept it hidden from school" (personal communication)*.

In some instances, adolescents may paradoxically react to this lack of understanding by hiding their mental suffering, in a desperate attempt to protect their unsupportive parents: *"I just did not want to tell [my parents] because I did not want them to worry or to feel guilty or something like that"*[53].

On the other side, parents who acknowledge the presence and severity of a mental disorder but aggressively insist on therapeutic approaches may prompt feelings of dehumanization: "*My parents keep saying this term that I have to be 'fixed' or 'cured', and I hate it because like it makes me feel like I'm not a person, as if I'm almost like an object or a disease*"[103].

Feeling restored by an emotionally supportive family

For many other adolescents, the familial environment may actually represent one of the most supportive settings. The emotional intimacy of a supportive family nurtures vital and positive coping strategies: "*Now I think she [the mother] has begun to understand. It is as if we can walk straight together. I do not feel guilty anymore, and it is easier to be honest when I struggle*"[104].

The feeling of being supported by the family consolidates a warm sense of security that helps adolescents engage with the challenges of living with a mental disorder: "*Whenever I have a problem, they [parents] give me a hand and help me succeed*"[90]. Within a supportive family, they feel able to talk freely and openly about their deepest experiences, thus alleviating their acute suffering and restoring a sense of normality: *"I don't always give in; I turn to my mum; she's like one of my biggest supporters in my life. We're very, very close… I'll go and sit with her and talk to her, and it slowly goes away"*[93].

The parents' perspective

Parents typically experience dramatic changes in their relationship with their unwell kids: "*Where is my daughter gone, because that's not her*"[105]. The onset of a mental disorder forces the parents to redefine their image of their kids[106], "*mourning the child who would have developed normally*"[107].

Parents may express an increasing difficulty in connecting with their kid's inner world, because of severe communication barriers: "*He doesn't talk to me*"[108]; "*He no longer wants to participate in any family things*"[105]. Accordingly, they experience a marked sense of loss[105].

Parents must "*learn how to parent in a completely different way*"[109,110], often negotiating a new balance between maternal and paternal roles[107] and establishing new parental rules[111]. This may include "*letting [the child] get away with things that I wouldn't have before probably*"[108]. It's a hard and unpredictable process of trial and error, frequently leading to frustration and feelings of helplessness: "*I changed the approach and tried to push a bit more and in certain areas, and then that didn't seem to be working and then, I don't know what the best way is*"[105]. Moreover, parents may feel the pressing responsibility to preserve their kids' emotional balance as much as possible[108].

The experience in the school and among peers

Perceiving the school as a magnifier of differences

Adolescents with a mental disorder often perceive the school as a fundamental but precarious environment. When they compare themselves with schoolmates, they feel profoundly different: "*[You] see other people… not being sort of freaked out and anxious or depressed whatever, you feel like 'why can't I be more like that?'*"[112].

Frequently, they feel forced to hide their true feelings from their peers: "*I could not show it to anyone because I never talked to my friends about my feelings*"[53]. This separates them from the surrounding social environment, leading to deep feelings of loneliness and incomprehension: "*You feel quite alone when you're growing up with things like that because there's not really anyone who understands it*"[112].

The vitality and fun that normally characterize the school environment fade away, replaced by feelings of exclusion and defeat: "*Because adolescents are supposed to have fun and hang out with friends at parties, but I kind of never feel like doing anything, and I wish I could enjoy things like before*"[90].

Negative relationships with teachers may further exacerbate the deep experience of loneliness and being different: "*[Teachers] treat me like a cute cat. They treat us like we're not human, like we're less*"[74]. Any teachers' attempt to support the individual can also be experienced as a direct confirmation of their personal ineptitude compared to their peers: "*We are different, that's a fact, but they treat us like we're different. Like we're more different to other people than we actually are*"[74].

Experiencing bullying from peers and teachers

Adolescents with a mental disorder frequently experience severe bullying[113], which further compromises their self-confidence and interpersonal trust: *"They took pleasure in hurting me, in seeing me suffer"*[114]. Because of bullying experiences, they may feel profound shame and embarrassment while at school: "*Me and a bunch of other kids had to go down at lunch to take [Ritalin], and it was kind of embarrassing… people saw me as the kid with ADHD, and they saw it as a bad thing"*[115].

The world of peers becomes a dangerous and unwelcoming place where they must be on guard: *"I'm quite suspicious, at least more than before, always a little apprehensive about who people are, their personality, what they really think"*[114]. The subjective experience of being bullied may be so dramatic that they may feel completely rejected, losing a sense of belonging ("*I felt rejected. No one liked me; none of my teachers liked me*"[90]) and eventually withdrawing from friendships and social interaction ("*Afraid of my friends sharing what I tell them to other people*", *personal communication*).

At the same time, they still long for vital friendship and social belonging. To overcome this situation, they may resort to a passive acceptance of bullying: "*I wouldn't want to stop being friend with them because I don't have any friends, so I kind of just suffered through it"*[115]. Sometimes, the experience of being bullied is transformed into self-blame, to make sense of the inner confusion and hurt that is elicited by dysfunctional relationships: *"I used to think it was my fault if I was mistreated by friends"*[104]; "*I didn't really try* *to be friend with anyone because I didn't trust myself to make good friends"*[115].

In other cases, adolescents with a mental disorder may suffer from their teachers' lack of understanding (*"It all comes down to lack of understanding. I felt like teachers did not know how to respond to people experiencing mental disorders"*, personal communication), or even bullying (*"One day he [teacher] just told me that I was going to fail and that I was a huge failure and I was never going to amount to anything… in front of the whole class"*[103]).

Experiencing peers as a vital support

For many adolescents with a mental disorder, however, peers may represent an important and positive resource. Feeling accepted by friends is described as destigmatizing, allowing the individual to regain a sense of normality (*"I told them, my close friends. They just said, "So what?" and they just looked at it like a cold, not like a disease"* [116]), and to dissipate feelings of shame and inadequacy (*"They weren't ashamed of it, so I started to not be ashamed of it either"*[116]).

In particular, being with friends who share a mental disorder is perceived as extremely beneficial to overcome the social isolation[117] (*"I'm not the only one going through this"*, personal communication), communicate personal experiences (*"My friends and I come together and speak about our experiences"*, personal communication), freely express complex emotions (*"We feel liberated; we get all our hatred out, all our anger, it feels good"*[114]), and improve their self-esteem (*"We share a lot of same feelings about things and I'm just able to really be myself"*[115]).

Peers' understanding may also alleviate their subjective suffering: *"When I feel that I am beginning to become anxious in school… then I can tell a friend, 'I do not feel okay at all right now'"*[104].

The experience in the social and cultural context

Feeling inadequate to the social norms and values

Adolescents with a mental disorder may feel inadequate in relation to the norms and values of their sociocultural context. For example, they may feel abnormal and even dangerous because of the beliefs socially attached to mental disorders: *"Like if you have a mental illness, you're not normal, you can't live a normal life… They think that they're going to catch it"*[118].

Others may feel inadequate because they perceive their mental disorder as an obstacle to achieving the social standards of a good life: *"I'm wondering a lot about my future, how to manage at school, if I get a good profession and if I reach my dreams instead of leaving them halfway"*[50]. To keep up with external pressures and social expectations, they may adopt a rigid conception of who they should be, silencing their mental health needs: *"As an adolescent, you end up adopting a very narrow view of yourself and the world when academic scores, building a career, and similar external achievements are ranked above mental wellbeing" (personal communication).*

Sometimes, the stress associated with school performance and striving to be socially successful exhausts their already fragile mental reserve: *"I have to be the best in my class. I'm a top athlete – doing sports at the highest level. It's so much pressure and expectations and… I must be ready to go to a party and be together with my friends… it's so much!"*[95].

Feeling stigmatized or supported by social media

Most adolescents with a mental disorder report using social media regularly as a way to interact with their social world: *"[Social media] keep you updated on the day-to-day lives of your friends and celebrities. And popular things that are going on"*[119]. They experience both negative and positive impacts of social media on their mental health.

For example, social media enhance comparisons of their suffering life with the apparently happy and successful accounts of their peers[119,120]: *"One thing that has impacted on my mental health is going on social media when feeling down, and you see all these posts of people living their best life, and you know you are not in that place. I'd wish my life could be like that" (personal communication).*

Another negative experience is the deeply stigmatizing, offensive and insensitive language that they may perceive on social media (*"They will call me crazy"*[51]), particularly if their daily life is exposed: *"Social media are easily accessible. The issue is that you can see it all day, every single day. Think of how many bad experiences and mean comments you'd see by scrolling" (personal communication).*

A common negative experience related to social media is the pressure to be constantly active online due to fear of "missing out": *"If I didn't have it [social media platform] I just think about all the things that I wouldn't see or know… there's so much pressure to have it and once you get it, you're basically stuck… it feels like you're stuck"*[120]. This is often linked to fears of sharing personal information, losing privacy, and reinforcing negative thoughts[119,120].

However, social media may also be perceived as a supportive resource for restoring some vital social networking and a sense of belonging to a community: *"There are communities of people with mental illness, where people share their experiences… so, on my side, it's been a positive experience" (personal communication).*

Social media may become a way of sharing experiences of being unwell across different communities, thus alleviating the sense of isolation and loneliness: *"It is difficult for me to talk to people, and then, social networks just help me because I'm able to contact certain people that I know will support me in different things, even though they might be far away from me"*[121].

In some cases, social media may actually represent the only positive support received: *"Most of my support system has been from social media" (personal communication).* They may also function as a powerful literacy means, allowing adolescents to get tailored information and empowerment: *"I've learned more about mental health online" (personal communication).*

The parents' perspective

Parents may experience great suffering because of the environmental stigma directed towards their kids: "*That hurt me... when other parents were saying to their child 'don't play with him*"[122]. Parents may feel "*distressed*" by the mental suffering of their kids [108], and at the same time feel helpless[105,106,108] as they do not have "*the right weapons"* to face the mental disorder[123]. Taking care of a kid with a mental disorder is experienced as *"mentally... and physically exhausting*"[105]. Parents frequently perceive themselves as *"alone as no one understands"*[124] and prefer to *"keep all"* to themselves[125,126].

Sometimes, parents report being indirect victims of the bullying experiences suffered by their kids: "*That upsets you as a parent when you know your child is being bullied or criticized*"[122]. They may feel particularly frustrated and guilty because they feel unable to protect their vulnerable kids from being bullied: "*A part of you [is] unable to withstand being with that child*"[122]. At the same time, parents may perceive themselves as a direct target of stigma, being blamed as *"unfit parents"*[122] ("*I always feel like I'm getting judged as a parent... that I'm not doing the right thing, or raising my child the right way*'"[122]), or being "*avoided*"[122].

The combination of stigma and bullying experiences may impair their self-esteem and constantly make them feel judged as bad parents[122]. The bad-parent labelling and stigma may occur not only in the community, but also within the family of origin: "*Close family was saying to me... that I created the problem*"[122].

Whatever the origin, stigma is inevitably perceived as burdensome ("*It made everything harder*"[122]), and parents may end up reducing social contacts ("*I do get asked... by friends, but I try to avoid it, only because I feel I have that stigma that they think I am a bad mum*"[122]). They may feel unwelcome at school, and may withdraw from collaborative and social events: "*I have opinions, and I want to make a contribution to things [but] I feel like I can't join them because I have a child who is difficult*"[122].

Under these intense pressures, parents may also desperately attempt to *"educate those people"*[122] and *"correct them and their 'ignorance'"*[122], becoming advocates for their kids' needs and, in this way, feeling reassured of being good parents[122]. Moreover, many parents experience an essential supporting role of the family of origin[107], or other families with the same problems, that can help "*to put [the kid's difficulties] in perspective*"[107].

THE LIVED EXPERIENCE OF ADOLESCENTS WITH MENTAL DISORDERS IN RECEIVING MENTAL HEALTH CARE

This section explores the lived experience of receiving mental health care in adolescents with a mental disorder. We describe these subjective experiences through seven overarching narrative themes: a) the experience of being diagnosed with a mental disorder, b) the experience of accessing mental health support, c) the experience of receiving psychopharmacological treatment, d) the experience of receiving psychotherapy, e) the experience of peer support and mental health activism, and f) the subjective experience of recovery. For a) and b), we also cover the parents' perspective.

The experience of receiving a diagnosis of mental disorder

Experiencing a threat to one's identity: surprise, denial, shame and secrecy

For adolescents, receiving a diagnosis of mental disorder is a very sensitive issue during a period in which identity is constantly being defined: *"It [the diagnosis] became the thing that defined me. It was the only thing I saw in myself, and everything was about that"*[127]. They often describe a negative impact on their identity; in particular, a feeling of surprise and disbelief: "*I was surprised and... I think that it made me tense because I had never thought about something like this*"[51]. In several cases, they show a strong rejection and denial: "*No, I can't be bipolar. That's just not me. I don't want to be it*"[116].

Denial is often accompanied by a desire to be like "normal" young peers: "*I don't want to be bipolar. I want to be normal... I'm sad. Why am I like this? Why did it have to happen to me?"*[116]. An intense feeling of shame often emerges: *"I was ashamed because I don't want to be bipolar. Who does?"*[128]. The intensity of the shame amplifies the uncomfortable feeling of being different: "*I had something [a diagnosis of mental disorder] like something was wrong with me. I was like different. That I was an outcast"*[128]. Shame, in turn, may lead adolescents to conceal their fragile condition: "*I don't like others to know about it. Because it's like none of their business, I just don't want them to know about it*"[116].

Sometimes the denial of the diagnosis leads to a cascade of decisions and behaviors that delay access to mental health care. In this context, the role of health care professionals in adequately and sensitively communicating the diagnosis is of vital importance, as it may otherwise elicit confusion and misunderstanding. For example, many young individuals report a lack of clear information and explanation about the implications of their diagnosis: "*They told me I had schizophrenia... but I didn't know what schizophrenia was; I didn't know that disease*"[106].

Finding a container for personal suffering

In several cases, the diagnosis of a mental disorder is preceded by a long period of difficulties and personal suffering, often tracing back to early childhood. As such, the diagnosis may be welcome as a meaningful container of the presenting problems (*"I took it well because I've always known that there was something different with me", personal communication)*, or as a way to relieve suffering (*"[Getting the diagnosis] was kind of comforting"*[127]).

Acceptance of the diagnosis is facilitated by appropriate and comprehensive communication with health care professionals: "*I got my diagnosis by a psychiatrist. He gave me enough information* *to understand..., and it was life-changing. It was new information, but he put it in a way that I can understand" (personal communication).*

The parents' perspective

Parents often experience their kid's diagnosis of mental disorder as "*a shock*"[106], "*an earthquake*"[106], or "*like being punched in the stomach*"[129]. The signs of their kids' difficulties may be "*little strange things*" hard to notice[56]. Sometimes external people (e.g., school personnel) are the first to draw parents' attention to these early problems[108]. In other instances, the parents "*never dreamed it was a medical condition*"[56], attributing the early anomalies to teenage behavior[108]: "*an extension of his personality, just a little bit sort of exaggerated*"[56].

In other cases, parents recognize the problems and feel "*prepared for... the diagnosis*"[129], but wait a long time before turning to professionals: *"You put up with it for a long time, and then there's a point when you break... when you refer yourself to mental health services; you waited till the last minute"*[130]. The diagnosis may be perceived as a relief[129], allowing the parent to make sense of things and "*have a reason for everything*"[109]. Parents may feel comforted by the fact that the professionals' understanding of their kid "*matched what [they] saw*" at home[129], and feel that the information received along with the diagnosis "*has been helpful to explain it to the rest of the family because trying to get it into words yourself and getting them to understand... that's the hardest part*"[129].

Parents may desperately look for external causal factors underlying the diagnosis: "*the dictates of today's society*"[123], "*the social context*"[123], "*our education system*"[105], and the media ("*Television..., social media... lead them to see themselves different from the world*"[123]). Alternatively, parents may look for internal causes, either organic or psychological: "*a chemical imbalance*"[123], a hormonal teenage phase[123], "*character*"[123], "*a loss of self-confidence*"[105].

Given the uncertain causal pathways of most mental disorders, parents typically struggle to identify an established cause, and might end up blaming themselves, considering the disorder genetic[123,131] or a consequence of exposure to their behavior[105,108]: "*Is it something I did... when I was pregnant, or during the younger years*?"; "*What could I have done to prevent it*?"[122]. A sense of guilt often accompanies the parents' elaboration of the diagnosis ("*I will always blame myself about that*"[122]), leading them to question their parenthood skills[122,132] ("*Maybe because we didn't understand how to raise a child well*"[125]).

Because of these concerns, parents may hide or downplay the diagnosis of mental disorder in their kids: *"He can access services... and people... can make accommodations for him, but... is he going to be treated differently?"*[74]. They may decide to hide it because "*the word mental in our community is very unacceptable*"[131] and to prevent their kids from being "*blackmarked*" at school[74], or even enrolled in special classes for disabled individuals[107,133].

The experience of accessing mental health support

Overcoming emotional barriers

The difficulty in accepting the diagnosis of a mental disorder frequently represents the first barrier to receiving help: *"I didn't accept what I had, and I didn't want any medicine"*[128]. Furthermore, many adolescents, once they have recognized their mental fragility, describe a variety of emotional barriers hindering the start of the treatment process.

The main help-seeking difficulty is related to embarrassment and shame: "*Sometimes I get embarrassed to talk to someone else*"[54]. For some adolescents, sharing their suffering is like adding to it, because it increases their sense of fragility: "*To share... is difficult because I feel vulnerable, and... kind of naked... feel stupid and embarrassed*"[95].

Some young people report a range of fears, including fear of violation of privacy (*"If people hear things and see things, then they'll discuss it with someone and eventually it will spread"*[134]), of not being understood ("*I don't want people to be like, oh, she wants attention*"[135]), or of being judged ("*I was scared of telling how I felt... because I thought they will judge me*"[135]).

Overcoming structural barriers

Adolescents may also experience access to mental health care as an obstacle race, because of a slow system with long waiting lists (*"I felt that you had to do something to get in here fairly quickly because there's such a demand for these services. Six months waiting list otherwise"*[118]), or an overly complicated care pathway that is difficult to navigate ("*Not knowing what services there are for certain things. It's just you go to one place and then oh no, we don't cover that here, you know, go to this place*"[134]).

Also, access to mental health care is not easily affordable for adolescents in many deprived areas: "*In Kenya, accessing mental health services is quite expensive, so there was that issue of 'am I going to get money, am I going to be able to see a psychiatrist'?" (personal communication).*

Feeling welcome, listened to and encouraged

For many other adolescents, receiving mental health care is a highly positive experience: "*I think here it's great. It's probably the best care I've ever had since my illness started. If I've got a problem, I just phone them and tell them, and they are out instantly. It is brilliant*"[136]. They feel welcome and know that they have a point of reference. This allows them to manage their negative emotions and symptoms better.

Easy access to mental health care enables them to experience that they are not a burden and that they really matter: *"Someone is taking care of me... maybe I am important after all"*[53]. In this context, the relationship with health care professionals may help them to feel that they are not being judged (*"He's easy to talk to, he's not one of those judgy people that I don't like"*[134]); that they are listened to (*"That time the doctor didn't give up but kept on seeing me every day of the week to find a solution. To understand me. He didn't just stick to the protocol for my treatment"*[137]); and that they are encouraged (*"It's nice that somebody says you're doing a good job – it makes you feel a little bit happier"*[129]).

Feeling lost and scared while transitioning from adolescence into adulthood

Adolescents transitioning into adulthood frequently feel lost and alone because of the two-tier split between children and adult mental health systems. A constant experience is the lack of information. Many do not know what to do, and feel lost and frightened: *"I wish someone had told me way sooner, like much more in advance, about what would happen… as opposed to being in the dark until then"*[138].

The lack of information may trigger uncertainty and fear of what would happen: *"I am feeling a lot better, but what happens in a few months if I am not? What can I do? Because I don't know what I should do now if I need someone"*[138]; *"Oh God, what's going to happen?"*[139].

In other cases, adolescents may experience profound feelings of ambivalence towards health care: *"I'm not sure how I feel. I don't really know about [the referral] enough to think much about it"*[138]. Moreover, lack of continuity in care may hinder the development of close and trusting helping relationships with professionals: *"You don't want to have to re-live… Re-living it every time brings back the pain… The fact that there's more than one person that knows about it is even scarier… And, then to have – you know – two or three new counsellors over a few years ends up destroying you"*[134].

The parents' perspective

Parents may also report emotional or structural barriers and negative experiences of mental health care access. They frequently feel that their concerns are dismissed without proper evaluation: *"[Psychiatrist believed that our daughter is] just angry and rebellious at home and not a serious threat to herself"*[140]. They may fear criticism about their parenting skills and express concern that their kids may be taken away from them: *"I was afraid they were going to call the mental health services and [demonstrate that]… I'm not able to take care of my son"*[140]. They may feel unaccepted: *"It was like the doctor just didn't seem to hear what I was saying"*[108]. They may perceive a lack of information and support: *"We were so frustrated… most of them said just go to an emergency room… that's so traumatizing"*[141].

These negative experiences may be amplified by structural barriers in accessing mental health care services: *"The waiting lists are so long, because there isn't enough staff and the staff are restricted due to funding"*[126]. Complex pathways to care may also be perceived as substantial obstacles: *"It's a lot of paperwork; there's a lot of stuff a person has [to do]… it was a challenge"*[126].

However, there are also positive experiences of accessing mental health care. Some parents feel welcome and fully supported: *"It was nice that someone saw his problems and took him seriously"*[130]. They may also report an important reduction in isolation as a result of the positive and reassuring experiences with mental health care: *"[The doctor] said it's okay, we've seen this before, you're not on your own, there is help. It was really reassuring"*[130].

The experience of receiving psychopharmacological treatment

Experiencing shame and fear of being labelled or different

The experience of receiving medication among adolescents with a mental disorder is highly variable. A range of emotions and feelings may arise, hindering drug treatment to the point of outright rejection: *"I don't want to take them at all"*[142]. Shame is the emotion that most contributes to rejection and poor compliance: *"I mean, it's really difficult… It totally can embarrass you if you have to take it in front of other people"*[116]. In addition to shame, there is also the fear of being judged and labelled, and of what others might say: *"Crazy. Psycho. Nuts. Cause that's what I heard from everyone else"*[116].

These negative emotions are reinforced by the perception of being different when pharmacological treatments are prescribed: *"I give up feeling normal by taking medication. I don't feel like a normal person"*[116]. Feeling different increases the sense of fragility and social isolation, while they desire to be "normal" like everyone else[116,128,143].

Improving social relationships and restoring emotions

On the other hand, adolescents may also describe positive experiences related to psychopharmacological treatment. When they accept medication, they may notice its positive effects on their relationships with family and friends: *"I'm happier. I used to spend all the time in my room, and now I'm upstairs with my family more. I spend more time with them"*[144]. Psychopharmacological agents may also be experienced as essential for restoring their social performance at school: *"In the past… I could not stay in the classroom. I could not even attend a virtual class. I did not want my name to appear there, and I was so anxious. The medicine has been very good for me"*[143].

There may also be a perception that medication improves their emotional reactions: *"I started taking medicine, and I would see a totally different person when I took the medicine. I mean, I wasn't so angry, and I was able to have a good time and laugh and just have fun"*[144]. Adolescents may also report that antipsychotics help to restore their sense of reality and normality: *"It is good because it definitely muted any kind of weirdness"*[145].

The experience of receiving psychotherapy

Experiencing a negative relationship and feeling not understood

Adolescents' experience of psychotherapy is greatly shaped by their relationship with the therapist. Some of them report negative experiences linked to not feeling understood: "*They [doctors] don't dig deep into the problems, what's really the matter with you, they don't do that at all… That's terrible, isn't it? I just felt they didn't really try to understand*"[136]. In some cases, suffering is experienced as being minimized by the therapists: "*[The doctor] thinks my illness is childish and just a way of getting attention, so he treats me like a child*"[136].

Sometimes, adolescents do not feel encouraged to talk about their problems and struggles, and feel that they are simply stuffed with medication: "*[Doctors] just give you medicine all the time whenever you aren't feeling good… they don't try and make you talk enough*"[136].

Feeling closeness and safety

On the other hand, adolescents may also describe positive experiences linked to feelings of closeness and safety with the therapist: *"She was affectionate, she was trustworthy, I would tell her something, and I was sure she would not tell anyone"*[146]. These experiences are especially related to instances in which the psychotherapy is perceived as personalized: "*What he did [the therapist] was something I needed, it surprised me, I thought he was just going to listen… But in reality, he gave me alternatives, things that would not occur to me"*[146].

Adolescents may particularly appreciate psychotherapy when it targets outcomes other than the presenting symptoms, restoring a deep feeling of being human ("*Sometimes you get scared of your feelings… However, when someone else is sitting there and telling you why she would be angry if she experienced that same situation… It is good to know that I am only human*"[104]) and of being a valuable person ("*The psychologist treats me as a person*"[136]).

The experience of peer support and mental health activism

Healing through healing

Adolescents feel that sharing their experiences is a way to help each other and to give new meaning to their fragile condition, overcoming stigma. Many of them describe how helping others affected by similar experiences makes them feel better and promotes a sense of belonging, by reducing feelings of being alone and abandoned: "*Peer support helps young people feel belonging, express themselves and improve self-help skills*" *(personal communication)*. This shared experience activates a two-way movement of benefits, which is perceived as rewarding: "*I am currently a volunteer at mental health research. It has helped me a lot in interacting with different youths facing different mental health problems, and I am happy I am able to share my experience" (personal communication).*

Voluntary work is viewed as a highly positive experience. Helping others allows adolescents to feel useful and valued. By spending time in service to others, they can bring structure to their lives and daily routines: "*It helps you get out of bed and also do something productive, so it helps with depression and stuff because you're actually doing something and seeing other people"*[147]. It is also an opportunity to find motivation to go on and push themselves to do something new: "*I'm not the type of person who would just have a conversation with you… I had to talk when I volunteered. I had to push myself out there*"[147].

The subjective experience of achieving recovery

Floating between self-acceptance and the looming shadow of relapse

Recovery may have different meanings for adolescents with a mental disorder. Many of them describe it in terms of learning to accept themselves: *"For me, recovery meant acceptance; accepting everything that I went through, that it is not my fault, being able to go on with my life and being productive, being able to see the sunshine. Being able to be confident and smile again*" *(personal communication)*; "*Recovery is accepting the things I can't change, and changing the things I can" (personal communication).*

Recovery may also mean separating their identity from the diagnostic label: *"[The diagnosis does not] define me anymore and I have skills that I can use to be the best version of myself"*[127]. It may also be described in terms of regaining autonomy and leading a more fulfilling life ("*Recovery to me means being able to live a productive and fulfilling life… socially, being able to interact with my friends, being able to come to work", personal communication)*, and rebuilding a sense of social connectedness (*"I rebuilt another social network and I was doing fine emotionally"*[127]).

On the other hand, the recovery experience may fluctuate, including negative emotions, especially the looming shadow and fear of relapse: *"I fear I'm back to square one"*[148]; *"[I fear] that things will deteriorate and I'll end up back here. I'd see that as defeat because you've battled for a long time to get out and then you just end up back; it's like you're starting back from square one"*[148].

DISCUSSION

This study describes the lived experience of adolescents with a mental disorder, covering both their subjective suffering and their positive accounts. The co-designing, co-conducting and co-writing approach adopted by the study has already been detailed in previous publications[21,22]. This approach allows personal experiences of mental disorders to emerge, minimizing exclusion and misrepresentation of the affected persons' perspectives[149]. In this study, we also integrated the parents' and carers' narratives, as applicable.

The study does not address any specific research hypothesis or whether the described experiences adequately represent the relevant mental disorders. We only highlight core (paradigmatic) ways by which adolescents experience their disorder subjectively and within the social context, and their experience of receiving mental health care. We identify common themes and sub-themes holding several implications at clinical, research and societal levels.

A first group of severe mental disorders, i.e. mood and psychotic disorders, are often characterized by experiences of change of one's personal identity, along with overwhelmingly intense emotions, and a distorted perception of the world. Adolescents typically find it difficult to communicate these experiences and, rather than seeking help, tend to conceal them, leading to delayed recognition of their problems. Converging evidence indicates that delayed recognition of mental health difficulties in young people with emerging mood and psychotic disorders is a key driver of missed preventive and early intervention opportunities and, therefore, of poor outcomes in their adulthood[150-153]. We hope that adolescents will recognize their experiences of mood and psychotic disorders in the words spoken by our experts by experience and, by doing so, will be more inclined to seek help and facilitate an early recognition.

Beyond help-seeking behaviors, early recognition of emerging mood and psychotic disorders in adolescents is also limited by the use of suboptimal assessment measures that risk overpathologizing potentially transient and clinically irrelevant experiences[154,155]. The core experiences of mood and psychotic disorders identified in this study could, therefore, represent innovative research material, which contributes to tailoring the next generation of assessment instruments for emerging mental disorders in adolescents.

A second group of disorders in adolescents (including ADHD and autism spectrum disorders) are largely characterized by experiences revolving around one's neurodiversity. This may be perceived and dealt with in a variety of ways[156], which have been very rarely explored up to now. We think that giving voice to these young people whose minds work differently from others corrects an epistemic injustice[149], while at the same time opening a new research avenue that can potentially expand our perspective of their conditions. Indeed, neurodivergent young people are often unfairly harmed as a social minority[157]: their story is frequently disvalued, silenced, ignored, distorted or misrepresented[158].

A third group of mental disorders in adolescents share, in different ways, feelings of lack of self-control and high impulsivity, described as experiencing the tsunami of an anxious body, losing control of one's anxious mind, and living in a shrinking and unpredictable box (anxiety disorders); controlling food to control oneself, and desperately searching for an idealized identity (eating disorders); feeling like a bottle full of rage, and feeling misunderstood and rejected (externalizing disorders). These experiences are characterized by a dynamic tension between adolescents' movement toward increased autonomy and their vulnerability to engage in impulsive and out-of-control behavior[159]. This contrast is neurobiologically associated with brain changes in the reward and self-regulating brain networks, that become unbalanced due to pubertal maturation. While pubertal hormones sensitize the brain's reward system, motivating the adolescent toward engaging in more sensation-seeking behaviors, the brain's capacity for self-regulation and inhibitory control matures more gradually over the course of early adulthood[160]. This neurobiological imbalance can also account for the frequent self-harm behaviors reported by adolescents, often described as the need to transform psychic into physical pain to control it, or shouting for help without words.

The latter call for help highlights the importance of exploring the lived experience of adolescents with a mental disorder in the wider society, another neglected research area up to now. Our adolescents described experiences such as suffering a painful lack of understanding within the family; perceiving the school as a magnifier of differences, and experiencing bullying from peers and teachers; feeling inadequate to the social norms and values, and feeling stigmatized by social media. However, they also reported experiences of feeling emotionally restored and supported by the family, perceiving peers as vital support, and feeling supported by social media, indexing the multifaceted and complex nature of each journey.

A dysfunctional parent-child interaction, along with genetic predisposition, has been historically identified as a key mechanism for the familial transmission of mental disorders[161], highlighting that the mental health of adolescents is to a large extent a "family affair"[161,162]. On the other hand, bullying from peers and teachers is a key driver of victimization and perceived stigma[163,164], which was described by our experts by experience as "*having worse consequences than the mental disorders themselves*"[165]. Overall, early traumatic experiences in adolescents emerge as the most robust transdiagnostic risk factor for the development of mental disorders later in adulthood[7,166]. We hope that our findings may thus inform educational approaches; for example, those focusing on parent or teacher training and literacy to improve youth's mental health[167,168], or anti-bullying interventions in the schools[113].

The lived experience of receiving mental health care in adolescents was also highly variable. Receiving a diagnosis of a mental disorder was experienced either as a threat to their identity – with feelings of surprise, denial, shame and secrecy – or as a useful container for their personal suffering. Accessing mental health support involved overcoming emotional and structural barriers, with frequent feelings of being lost and scared, particularly while transitioning from adolescence into young adulthood. We hope that the latter experience may prompt stakeholders and policy makers to prioritize creating youth-friendly mental health services[169-171]. These services may prevent many adolescents from falling into the cracks of the two-tier health care system split[9].

With respect to the experience of receiving specific treatments, adolescents variably described feelings of shame and fear of being labelled or different, or improved social relationships and restored emotions (when receiving psychopharmacological treatment), and of suffering negative relationships and feeling not understood, or feeling closeness and safety (when receiving psychotherapy). The nature of these experiences was largely influenced by the health care professionals' communication skills and attitudes. Peer support and mental health activism were more consistently associated with positive experiences of recovery through healing, restoring networks and a sense of purpose. The adolescents' journey through mental disorders was overall highly variable, and their ultimate experience of recovery was characterized by an unpredictable floating between self-acceptance and the looming shadow of relapse.

It is evident that there is no such thing as a uniform experience of the various mental disorders in adolescents, but rather a plurality of individual experiences. This study addressed these lived experiences' variability, complementarity, and even contrasting nature. We considered broad diagnostic groupings, because splitting the lived experiences across specific diagnostic categories would have rendered the analytic task unfeasible. Future studies could better focus on specific sub-diagnostic constructs, for example, by exploring the differential lived experiences of specific autism spectrum disorders such as Asperger's syndrome.

The evidence reviewed here has been critically extracted (although we started with a defined search string, as indicated above). In line with our protocol and with previous publications in this series[21-23], we did not plan to report any quantitative data.

In conclusion, this study is a distillate of the subjective experiences of adolescents from a wide range of backgrounds and cultures, integrated with insights from leading youth mental health academics. We hope that this work will contribute to raising the attention of stakeholders and citizens to the challenge of public youth mental health, because "the neglect of youth mental health is a form of self-harm that society has inflicted on itself"[172,173].

Understanding the lived experience of poor mental health among adolescents can help us address its major consequences in terms of lower educational attainment, increased health care costs, substance abuse, violence, self-harm and suicide[152]. The voices of young experts by experience presented in this study may be instrumental in catalyzing the design and implementation of a new youth mental health framework to maximize the potential of emerging generations globally[174,175].

We also hope that the themes and sub-themes detailed in this study can be used to train health care professionals and improve the mental health literacy of family members and caregivers, reducing stigma related to seeking help.

We hope that adolescents with mental health problems worldwide can access this study and feel less alone, isolated or stigmatized, by recognizing their own suffering in the words reported by their peers. Ultimately, we hope that this co-designed, co-conducted and co-written journey helps us maintain our commitment to protecting adolescents' fragile mental health, and help them develop into a healthy, fulfilling and contributing adult life.

ACKNOWLEDGEMENTS

A. Estradé, C. Esposito, R. Rosfort, I. Basadonne, M. Mancini and G. Stanghellini contributed equally to this work.

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DOI:10.1002/wps.21189

What's in a name? Mental disorders, mental health conditions and psychosocial disability

The constitution of the World Health Organization (WHO), adopted upon its founding in 1948 and now a part of its treaty arrangement with 194 member states, defines health as "a complete state of physical, mental and social well-being and not merely the absence of disease or infirmity"[1]. Clearly, WHO's founders intended to include mental health as a part of health, although they did not define it explicitly.

The WHO provided a more expansive definition of mental health in the 2022 World Mental Health Report: "a state of mental well-being that enables people to cope with the stresses of life, to realize their abilities, to learn well and work well, and to contribute to their communities"[2]. This definition suggests that mental health is not only more than the absence of mental disorders, but depends in part on access to opportunities to achieve one's potential.

These positive aspects of mental health – for individuals and for populations – are therefore construed as falling within the WHO's mission in a way that builds on the initial definition of health provided more than 75 years before. Health promotion, protection of vulnerable populations, and mitigation of social and other determinants that drive health inequities are fundamental to the global public mental health approach, although the World Mental Health Report acknowledges that responsibility for some of the steps critical to improving mental health falls outside the health sector.

The WHO's constitution also tells us that two of the twenty-two core purposes for which the organization was founded are "to establish and revise as necessary international nomenclatures of diseases, of causes of death and of public health practices", and "to standardize diagnostic procedures as necessary"[1]. The most important realization of these two constitutional functions throughout WHO's history has been the International Classification of Diseases (ICD). The 11th revision of the ICD (ICD-11) was approved by the 72nd World Health Assembly, comprising the Ministers of Health of all 194 WHO member states, in May 2019. The Assembly's approval is required because the ICD confers obligations on WHO member states, and such approval underscores and contributes to the ICD's considerable force and importance as an aspect of global health policy.

The ICD-11 defines mental disorders as "syndromes characterized by clinically significant disturbance in an individual's cognition, emotional regulation or behaviour that reflects a dysfunction in the psychological, biological or developmental processes that underlie mental and behavioural functioning; these disturbances are usually associated with distress or impairment in personal, family, social, educational, occupational or other important areas of functioning"[3].

However, except when reporting epidemiological data, the World Mental Health Report uses the term "mental health conditions", described as "a broad term covering mental disorders and psychosocial disabilities; it also covers other mental states associated with significant distress, impairment in functioning, or risk of self-harm"[2]. Thus, mental health conditions comprise symptoms and experiences associated with psychological distress or functional impairment, whether or not they meet the diagnostic requirements for specific mental disorders. They include, for example, acute stress reactions, personality difficulty, hazardous substance use, and burnout, which the ICD-11 does not classify as mental disorders but rather as "factors influencing health status or encounters with health services". Based on a dimensional conceptualization of mental health, the term "mental health condition" encompasses a portion of the population that would likely benefit from public policy and systems interventions, including population-based health promotion and prevention efforts, rather than treatment aimed at specific mental disorders.

Mental health professionals and policy makers may find the concept of "mental health condition" conceptually and practically useful in encouraging people to seek the help they need and far too few receive. Some subthreshold conditions have been shown to be as impairing as corresponding above-threshold mental disorders[4], and, in the context of a persistent and progressive disorder, early identification may provide an important opportunity for effective treatment[5]. On the other hand, available data suggest that the ability of subthreshold presentations to predict above-threshold mental disorders in the general population is rather low, and varies substantially by disorder[6]. The use of the term "mental health condition" may also raise questions about the value of investing in mild and subthreshold conditions that are imprecisely and poorly defined and even more common than mental disorders, which could complicate discussions about coverage and reimbursement, and potentially lead to a recapitulation of the arguments historically raised in opposition to insurance parity between mental disorders and physical diseases.

The World Mental Health Report clarifies that the term "mental health condition" was used in an effort to bring together the widest possible group of stakeholders, some of whom viewed the term "mental disorder" as stigmatizing. However, stigma can migrate from one term to the next almost as soon as the new term catches on. In addition, given that these terms are meant to apply to the global context, the semantic distinctions between them may not be meaningful in languages other than English. The translation may be the same for both terms, or their connotations may be different across languages. For example, *condición* in Spanish often refers to intrinsic and stable characteristics, whereas *trastorno* (the term used for "disorder") is closer to a disturbance or upheaval which may be temporary. Therefore, in some languages, "mental health condition" may be experienced as more stigmatizing than "mental disorder".

The second component of the World Mental Health Report's definition of "mental health condition" is "psychosocial disability", which "arises when someone with a long-term mental impairment interacts with various barriers that may hinder their full and effective participation in society on an equal basis with others"[2]. This definition is consistent with WHO's International Classification of Functioning, Disability and Health (ICF)[7], which describes disability as the result of the interaction of individuals who have a health condition with their environment, influenced by the nature and severity of the health condition, the characteristics of the person, and the physical and social characteristics of the environment.

Although the World Mental Health Report uses the term "psychosocial disability", in fact the impairments, activity limitations and participation restrictions experienced by people with mental disorders are not limited to the psychosocial domain. The Report links the term to the United Nations' Convention on Rights of Persons with Disabilities[8], which has been a powerful tool for dismantling discriminatory attitudes, actions and laws that contribute to human right violations among people with mental disorders, and for redressing physical, attitudinal, communication, social and legal barriers to their complete self-determination and participation in society. However, some disability rights advocates go considerably beyond that, arguing that the construct of "psychosocial disability" should replace the conceptualization of mental disorders as problems that should be clinically defined and treated. This view emphasizes acceptance and provision of support and accommodations, and sometimes positions the "medical model" as the source of human rights violations[9]. WHO's use of the term, however, is not an endorsement of an anti-psychiatry stance.

In the context of the terminology discussed above and the trends it represents, psychiatrists and other mental health professionals will likely continue to be primarily focused on the identification and treatment of mental disorders. They will also be increasingly called upon to collaborate with, teach and supervise other personnel involved in the mitigation of mental health conditions through population-based health promotion, protection and prevention efforts, as well as the provision of lower-intensity and less complex interventions (e.g., through "task shifting" initiatives).

We can align ourselves more fully with a global public mental health approach by expanding and deepening our focus on the impact of our interventions on functional status, particularly as it relates to self-determination and social participation, and on the mitigation of social determinants of health in order to reduce health inequities in our communities and around the world.

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The author would like to thank K. Revankar for his assistance in preparing the manuscript.

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DOI:10.1002/wps.21190

The value and limitations of self-administered questionnaires in clinical practice and epidemiological studies

In the past few decades, there has been a proliferation of self-administered questionnaires aimed to assist clinicians in improving the identification of various disorders, and researchers in estimating disorder prevalence rates in community-based epidemiological settings. Most of these questionnaires focus on a single disorder, such as major depressive disorder, bipolar disorder, or generalized anxiety disorder. A minority evaluate a range of the most common disorders encountered in outpatient mental health settings.

Self-administered questionnaires are not a substitute for an interviewer-based diagnostic evaluation. They are *screening instruments*, and their use represents the first phase of a two-stage diagnostic procedure. The purpose of a screening test is to cast a broad net to ensure that most patients with the disorder are captured in that net. Thus, a screening test is intended to reduce the frequency of missed diagnoses. That test is expected to be followed by a more definitive diagnostic assessment, an evaluation that is generally more expensive and/or invasive than the screening procedure. In psychiatry, a self-administered screening questionnaire is intended to be followed by a diagnostic interview. In studies of the performance of screening questionnaires, a semi-structured interview is the usual "gold standard".

The two most commonly reported statistics when describing the performance of a screening measure are sensitivity and specificity. Sensitivity refers to how well the test identifies individuals with the disorder, whereas specificity refers to how well the test identifies individuals without the disorder. Two other statistics important in understanding a screening test's clinical utility are positive and negative predictive value. Positive predictive value refers to the probability that a person who screens positive on the test has the disorder. Negative predictive value refers to the probability that a person who screens negative on the test does not have the disorder. Positive and negative predictive values are less commonly used to describe a screening test's performance, because these statistics are influenced by the prevalence of the disorder in the sample studied.

From a clinical perspective, it is most important that a screening measure has good sensitivity, and corresponding high negative predictive value. With high negative predictive value, the clinician can be confident that when the test indicates that the disorder is not present there is little need to inquire about that disorder's presence. False positives (i.e., persons who screen positive but do not have the disorder) are less of a problem for a screening questionnaire, because their major cost is the time a clinician takes to determine that the disorder is not present. Presumably this is time clinicians would have nonetheless spent for the same purpose had they conducted a comprehensive interview.

From an epidemiological perspective, it is most important that the self-administered questionnaire provides an accurate estimate of the presence of a given condition. However, when questionnaires are used in this manner, the studies should refer to the prevalence of *symptoms* rather than *disorder* (e.g., prevalence of depressive symptoms rather than depressive disorder). The prevalence of the disorder should be assessed by the subsequent use of a diagnostic interview.

Self-administered questionnaires for psychiatric disorders yield a continuous distribution of scores, and the developers of these instruments typically recommend a cutoff score to identify individuals who have screened positive. A major problem with the research using these questionnaires is that many scale developers take a case-finding rather than a screening approach in deriving the cutoff score to indicate which patients have screened positive. That is, investigators select the cutoff that maximizes agreement with a diagnostic standard (such as a semi-structured interview). From a screening viewpoint, a more appropriate approach is to select a cutoff that prioritizes a scale's sensitivity, so that diagnoses are not missed. A review of 68 reports of the performance of the three most researched screening scales for bipolar disorder found that only 11 (16.2%) studies recommended a cutoff that prioritized the scale's sensitivity[1].

The failure to appreciate the difference between case-finding and screening has led to inappropriate conclusions from studies using screening measures as diagnostic proxies. For example, a study of the impact of borderline personality disorder (BPD) on the response of depressed patients to electroconvulsive therapy (ECT)[2] used the McLean Screening Inventory for BPD (MSI-BPD) to "diagnose" the personality disorder. A summary of the performance of the MSI-BPD found that across studies the scale had a sensitivity of 80% and a specificity of 66% at the cutoff recommended by the scale's developers[3]. When this is taken into account, along with the prevalence of BPD in the sample, an analysis of this study suggested that the majority of the patients whom the authors considered to have BPD would not receive this diagnosis if administered a diagnostic interview. In other terms, the screening scale's positive predictive value was well below 50%. Therefore, valid conclusions about the efficacy of ECT in depressed patients with comorbid BPD cannot be drawn from a study using a screening measure to "diagnose" the personality disorder.

Studies of community samples have used screening questionnaires for bipolar disorder to estimate the prevalence of this disorder, the psychosocial morbidity associated with it, the frequency of the disorder's underdiagnosis, and the frequency of its undertreatment with mood stabilizers and overtreatment with antidepressants[4,5]. None of these studies discuss the limited positive predictive value of bipolar disorder screening scales in the general population[6]. None of these reports note that most individuals who screened positive for bipolar disorder would not be diagnosed with the disorder if interviewed (because the positive predictive value is less than 50%). Thus, the public health concerns raised in the discussion sections of these studies are based on misconstruing screening instruments as diagnostic measures.

More recently, online surveys based on self-administered questionnaires have been used to assess the psychological impact of the COVID-19 pandemic and of the public health restrictions imposed to limit the spread of infection. A PubMed search on November 24, 2023 on the terms "COVID-19" and "depression" yielded 16,026 citations. In almost all of these studies, depression was assessed by self-administered questionnaires. The literature has been sufficiently extensive to generate meta-analyses of the prevalence of depression during the pandemic in specific populations such as health care workers, pregnant women, and college students. Similarly, meta-analyses of the prevalence of depression have been conducted in various geographic regions of the world and have examined factors impacting that prevalence. The results of these studies have been used to influence public health discussions related to the funding of mental health services. However, screening questionnaires for depression, such as the Patient Health Questionnaire-9 (PHQ-9) – the self-report questionnaire most frequently used in these studies – significantly overestimate the prevalence of depression compared to diagnostic interviews[7]. Again, this is not a problem with the questionnaires themselves, which are designed to identify individuals who *might* have a disorder, while the subsequent use of a diagnostic interview is expected to distinguish true cases from false positives. The problem is with the interpretation of the results based on screening instruments.

When our clinical research group developed the Psychiatric Diagnostic Screening Questionnaire (PDSQ), we intended it as a diagnostic aid to be used in clinical practice to reduce underdiagnosis of disorders comorbid with the principal diagnosis and improve clinicians' efficiency in conducting the initial diagnostic evaluation[8]. Consequently, we recommended that a cutoff resulting in a sensitivity of 90% be chosen when using the scale in clinical practice, rather than a cutoff that optimized agreement with a diagnostic standard.

The bottom line is that a self-report questionnaire with high sensitivity and negative predictive value can be a valuable tool in clinical practice by guiding the clinician towards inquiry about disorders on which the patient screens positive (thereby reducing missed diagnoses) and identifying disorders that are unlikely to be present and thus requiring little or no inquiry (thereby saving the clinician time). In epidemiological studies, screening instruments can give accurate prevalence estimates if the cutoff point is appropriate, but the findings should be viewed as estimates of the prevalence of symptoms of a disorder rather than the disorder itself. Using expressions such as "prevalence of depression" or "prevalence of anxiety" (instead of "prevalence of depressive symptoms" or "prevalence of anxiety symptoms") may generate misunderstandings – in particular, an overestimation of the clinical and public health implications of the findings.

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DOI:10.1002/wps.21191

Anomalies of language in schizophrenia: a trajectory of mathematical and computational analyses

Disturbance in language production is a core feature of schizophrenia that has been recognized for more than a century, beginning with Kraepelin's and Bleuler's descriptions of decreases of coherence in spoken language, characterized by derailment and loosening of associations, and a relative poverty of speech. For many decades, the study of language in schizophrenia has remained primarily descriptive, culminating in Andreasen's heuristics of positive (disturbances in coherence) and negative (disturbances in complexity) thought disorder in the 1970s.

In the 1980s, Hoffman used a mathematical approach to characterize the misapplication of rules for sentence and discourse formation seen among individuals with schizophrenia, emphasizing semantic relationships between both adjacent and non-adjacent sentences. He developed formal criteria for a "strong hierarchy" of sentences, whose violations would constitute decreases in coherence, that he found to be highly prevalent in schizophrenia[1]. He subsequently replicated this finding, showing that individuals with schizophrenia have only small or deficient sentence hierarchies, whereas individuals with mania have frequent shifts among large and intact sentence hierarchies.

Artificial intelligence was first used to model reduced coherence in speech in the 1990s. Garfield and Rapp[2] showed that violations of specific rules in artificial semantic networks could replicate disturbances of spoken language in schizophrenia. Hoffman induced schizophrenia symptoms by reducing connectivity in neural network simulations of parallel, distributed processing systems. Further, he built a computational model of the disorder, finding that deficits in prediction error signaling had the best fit for the pattern of breakdown found in narrative coherence[3].

In the 21st century, there has been an increasing use of large language models to *quantify* discourse coherence in schizophrenia. Mota et al[4] were creative in the application of speech graphs to transcripts of spoken language, replicating Hoffman's findings with respect to deficits in schizophrenia distinct from those in mania[4].

In the past decade, the use of automated natural language processing (NLP) to characterize abnormal spoken language in schizophrenia has grown tremendously, extending to include psychosis prediction, such that automated NLP analyses of spoken language have been included in the Accelerating Medicines Partnership in Schizophrenia (AMP SCZ), a large international collaboration that aims to develop multimodal psychosis prediction among at-risk individuals, who notably speak diverse languages[5].

DISCOURSE in Psychosis is another global initiative launched in 2020 to promote international collaboration in studying language disturbances in psychosis across cultures and languages, with harmonization of methods used to elicit spoken language, so as to create large multilingual datasets for analysis (https://discourseinpsychosis.org).

Archived data from these consortia can be used to address key questions in the use of NLP to study language impairment in schizophrenia and its risk states, across languages and cultures.

A first question is methodological, i.e., what is the optimal way to elicit language. We use open-ended interviews, to allow for sufficient speech flow to observe decreases in coherence, and to create the ecologically valid context of a dyadic social encounter. This approach also enables the study of other communication modalities in tandem, including acoustic features, pauses, face expression and gesture, with data from both individuals in the dyad being informative.

Another key question regards the generalizability of findings across languages and cultures, and how language-specific features may be informative. For example, in a large cross-linguistic study of schizophrenia patients (and controls) – who spoke Danish, German or Chinese – only second-order coherence (i.e., the similarity between phrases separated by another intervening phrase) robustly generalized across languages, while other measures of coherence did not, for unclear reasons that require further study[6]. In another study of at-risk individuals in Shanghai, both Mandarin-based and English-based NLP methods captured intercorrelated decreases in language-specific coherence (and adjective use), but only Mandarin-based NLP captured greater use of "localizers" (e.g., *gongzuo-shang*, "during work"; or *liangge-ren-zhijian*, "between two people") in the at-risk group[7]. Further, while it is known that the abnormal use of referential noun phrases is common in schizophrenia across languages, this could only be documented in a study conducted in Turkish-speaking patients[8]. Both AMP SCZ and DISCOURSE in Psychosis offer the opportunity for further cross-linguistic studies, including in other European and Asian languages.

These and other datasets also allow to explore the phenomenology of language disturbance in schizophrenia and its risk states beyond coherence and complexity. For example, sentiment analysis can be used to assess the valence and emotional tenor of text. Using a picture description task (positive, negative, neutral) to elicit narrative and speech graph analysis, the connectedness of speech among individuals with first-episode psychosis was found to be directly correlated with the use of positive emotional words. In another study, sentiment analysis was used to identify the emotional tenor of spoken language in open-ended interviews with at-risk individuals, finding greater semantic similarity to "anger" in those who had concurrent suicidal ideation[6].

In addition to language, the acoustics of spoken language in the schizophrenia spectrum can be assessed, including dysfluencies, timbre/quality, energy/loudness and pause, as well as face expression and gesture in the context of interview[6]. This yields rich multimodal time series of data that can be used to assess incongruence between different modalities (inappropriate affect) and attunement between conversation partners in language and face expression, indicative not only of psychiatric illness but also of therapeutic alliance.

Now we are in the new era of generative large language models (GLMs), which has very significant implications for the study of language (and communication behavior) in schizophrenia. We have used large language models for NLP analyses for fifteen years, and they were silent, but now they can speak. The development of generative artificial intelligence, in particular chatbots, brings forth the notion of language as fundamentally interactive, intersubjective and cultural. Can GLMs be used not only to measure or quantify features of language, but also to model impairments and then intervene and remediate? In an update to Hoffman's computational approach, GLMs have been used to model the language impairment of schizophrenia. In a recent study[8], thought disorder was simulated in narratives using GLMs by increasing the stochasticity of word choice and limiting the model's memory span, with both disturbances decreasing sentence-level coherence.

Finally, since self-experience and behavior are constructed through language, language disturbance may represent a constitutive aspect of schizophrenia, and its remediation may be used to treat schizophrenia more broadly. In 1993, Hoffman hypothesized that abnormal discourse planning in schizophrenia leads to both decreased coherence in speech and increased involuntary inner speech. However, he also noted that there were some individuals who heard voices but had coherent speech, albeit relatively simple and rehearsed. He hypothesized that these individuals might compensate for impaired discourse planning by reducing their language output and complexity. He developed a "language therapy" for these "counterexample" patients, which was successful in both improving their discourse planning and reducing their hallucinations[9]. This is an intriguing but small study for which there have been no efforts at replication.

We believe that the use of GLMs may promote new avenues of research on the nature of anomalies of language in schizophrenia, on their meaning as a constitutive aspect of the disorder, and on the possible interventions on these anomalies and consequently more broadly on the disorder.

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DOI:10.1002/wps.21192

Improving the approach to LGBTQ persons in mental health care settings: a clinician's perspective

In 1974, the American Psychiatric Association (APA) removed the diagnosis of homosexuality from the DSM-II[1,2]. In 1990, the World Health Organization (WHO) followed suit, removing the homosexuality diagnosis from the ICD-10[3]. In 2019, the WHO went a step further and removed the diagnosis of "transsexualism", now renamed "gender incongruence", from the ICD-11 chapter on mental disorders. By placing gender incongruence in a new chapter called "Conditions related to sexual health", the ICD sought to destigmatize transgender individuals in the 21st century, much as the APA destigmatized gay and lesbian people in the twentieth [4,5].

These depathologizing changes, which reflect and integrate changing cultural beliefs and values regarding sexual orientation and gender identity, have shifted the mental health mainstream's clinical focus in working with lesbian, gay, bisexual, transgender and queer/questioning (LGBTQ) persons. Historically, psychiatrists and other mental health professionals spent many psychotherapy sessions trying to determine what caused homosexuality, or gender incongruence, in unsuccessful efforts to "cure" these persons. However, two people having a conversation in a room will never discover the "cause(s)" of anyone's sexual orientation or gender identity[6]. Today, it is acknowledged that the "determinants" of any sexual orientation (homo-, bi- or hetero-) or gender identity (transgender or cisgender) remain unknown.

Consequently clinicians, instead of seeking to find out "why" persons are LGBTQ in efforts to change them, have now shifted focus to thinking about "how" to help these individuals more openly and adaptively live their lives as LGBTQ persons.

This shift was embodied in the US Institute of Medicine's landmark report *The Health of Lesbian, Gay, Bisexual and Transgender People*[7], which highlighted the need for more research, including studies on the role of social influences on the lives of LGBTQ people and how to address inequities in their health care. While research has been done in the last decade, more is needed. As clinicians await the results of further research, there are some suggestions that the individual practitioner can follow to improve the approach to LGBTQ persons in mental health care settings.

First, many LGBTQ persons report experiencing disapproval, discrimination and even abuse in clinical settings. Consequently, they may avoid medical care if and when they can. And, when unable to avoid care, they may be reluctant to reveal their sexual orientation or gender identity without clear evidence of a clinician's non-judgement and acceptance.

This requires clinicians, in doing evaluations, to not automatically presume that all individuals, couples or members of families are heterosexual or cisgender. When inquiring about relationships, it is best to ask open-ended questions without presuming that one knows the gender of a patient's partner. For example, in many Western countries, and increasingly in other parts of the globe, not all marriages are heterosexual. Patient self-report intake forms should allow for responses regarding diverse sexual orientations, gender identities and family arrangements.

Recognition of alternative family and social relationships is particularly important when psychiatrically evaluating LGBTQ persons in emergency departments and acute inpatient settings. For patients living in communities and cultures that accept their identities, contact with an LGBTQ person's social support system is routine. However, in places and cultures where homosexuality and transgender presentations are less accepted, recognition by clinicians may be challenging.

Yet, clinicians should keep in mind that the person or people who know most about a patient's mental state and function may not have a state-recognized legal relationship. Consequently, it may be necessary to obtain information from them to identify potential sources of a patient's problems. Ideally, in working with LGBTQ populations, it should be the patients' well-being, not the state, that determines who should be contacted and spoken with.

In some countries and communities, it is increasingly common for LGBTQ patients to seek out mental health practitioners who identify publicly as members of that community. Although practitioners since the time of Freud have been cautioned about self-disclosing to patients, openly LGBTQ psychiatrists are increasingly present in many places. Today, they are in a unique position to advocate for improved services for the patient populations they treat[8].

Violence perpetrated against LGBTQ individuals is common across cultures and may lead to post-traumatic stress disorder, depression, and a range of other mental health problems. Perpetrators of anti-LGBTQ violence may include strangers, family members, co-workers and sometimes authority figures.

Complicating matters, those who experience violence, or sexual or domestic abuse, may not wish to report their experiences or seek help, due to fear that disclosing their sexual or gender identity may elicit judgmental responses – and even harassment – from police or social service workers. Ideally, clinicians sensitive to this reality can advocate for fair treatment of LGBTQ patients who have experienced violence and are dealing with insensitive bureaucracies.

Even in the absence of violence, clinicians should be sensitive to patient anxieties regarding the ubiquity of anti-LGBTQ attitudes, sometimes referred to as "minority stress"[9]. Patients may feel misunderstood when clinicians deny or minimize the extent to which this phenomenon colors their lives and affects their self-esteem.

The most severe expression of anti-LGBTQ attitudes may be seen in increased rates of suicidal ideation among LGBTQ populations, particularly among young people who are sorting out their sexual or gender identities. LGBTQ youth often hide their sexual or gender identity concerns from parents, and may not readily turn to them for support. In the US, for example, this issue is exacerbated in socially conservative states where efforts to identify the mental health needs of LGBTQ youth are regarded as "recruitment" or "grooming". Psychiatrists treating LGBTQ young people need to be aware of the sociocultural conditions that may exacerbate their patients' psychological distress.

In conclusion, it is not unusual for LGBTQ patients to face stigma and discrimination in their families, their communities and in the wider world. These experiences have mental health consequences which clinicians often encounter. One way to mitigate this stress is by demonstrating to patients, in both words and deeds, that they will not have to face stigma and discrimination in the clinical setting. This is a task which any ethical psychiatrist can and should be able to perform.

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DOI:10.1002/wps.21193

Philosophy of psychiatry: theoretical advances and clinical implications

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Work at the intersection of philosophy and psychiatry has an extensive and influential history, and has received increased attention recently, with the emergence of professional associations and a growing literature. In this paper, we review key advances in work on philosophy and psychiatry, and their related clinical implications. First, in understanding and categorizing mental disorder, both naturalist and normativist considerations are now viewed as important – psychiatric constructs necessitate a consideration of both facts and values. At a conceptual level, this integrative view encourages moving away from strict scientism to soft naturalism, while in clinical practice this facilitates both evidence-based and values-based mental health care. Second, in considering the nature of psychiatric science, there is now increasing emphasis on a pluralist approach, including ontological, explanatory and value pluralism. Conceptually, a pluralist approach acknowledges the multi-level causal interactions that give rise to psychopathology, while clinically it emphasizes the importance of a broad range of "difference-makers", as well as a consideration of "lived experience" in both research and practice. Third, in considering a range of questions about the brain-mind, and how both somatic and psychic factors contribute to the development and maintenance of mental disorders, conceptual and empirical work on embodied cognition provides an increasingly valuable approach. Viewing the brain-mind as embodied, embedded and enactive offers a conceptual approach to the mind-body problem that facilitates the clinical integration of advances in both cognitive-affective neuroscience and phenomenological psychopathology.

Key words: Philosophy of psychiatry, naturalism, normativism, scientism, reductionism, values-based care, pluralism, mind-body problem, embodied cognition, enactivism

(World Psychiatry 2024;23:215–232)

Work at the intersection of philosophy and medicine makes an important contribution by considering key metaphysical issues (e.g., what is the nature of disease?), epistemological questions (e.g., how do we determine the validity of diagnostic concepts?), and ethical matters (e.g., how does disease impact personhood?). Analogous questions arise at the intersection of philosophy and psychiatry. Since ancient times, implicit and explicit responses have had a crucial influence on clinical practice. In the West, for example, Aristotle's reply to these questions involved a notion of the "golden mean", while in the East an approach emphasizing concepts of *yin* and *yang* was developed – these frameworks were employed to understand disease and deviant behavior, and have influenced clinicians since[1,2].

Advances in science after the Enlightenment raised new conceptual questions about medicine and psychiatry. K. Jaspers is a particularly seminal figure in the history of philosophy of psychiatry; he not only wrote a key textbook of clinical psychiatry (*General Psychopathology*), but also advanced ideas about how best to conceptualize and research mental disorders[3]. His approach has had an enduring and substantial influence on clinical concepts and practice[4]. In recent decades, these questions have received increasing attention, with the emergence of professional societies and conferences, as well as journals, textbooks, and book series specifically devoted to philosophy and psychiatry[5-9].

An influential literature has emphasized the various competences that health care professionals should acquire[10]. More recently, the notion of "conceptual competence" has been proposed. In health care, conceptual competence refers to "the transformative awareness of the ways by which background conceptual assumptions held by clinicians, patients, and society influence and shape aspects of clinical care"[7]. These assumptions relate to a range of issues, including concepts of disease, professional values, causal explanations, and the mind-body problem. Here we aim to bring attention to and emphasize the importance of conceptual competence for psychiatry.

In the health care sciences, there has been growing attention to evidence-based approaches, and state-of-the-art reviews are expected to synthesize the literature in a rigorous way[11]. In philosophy, there is an ongoing debate not only about the parameters of good philosophy, but also about whether the field actually makes progress over time[12,13]. In this paper, we focus on three areas at the intersection of psychiatry and philosophy, exemplifying a broad range of conceptual debates in the field, which suggest that some progress has indeed occurred – if not in resolving all conceptual issues, at least in articulating them clearly – and which have particular relevance for clinicians.

We begin by considering responses to the key question of the nature and boundaries of psychopathology, an issue that has long been at the core of philosophy of psychiatry. We then move on to consider questions about the nature of psychiatric constructs and explanations in general, and about how best to think about the brain-mind relationship in particular. In outlining the advances that have been made, and their clinical implications, we argue that there has been a growing and useful emphasis in the field on soft naturalism, on explanatory pluralism, and on embodied cognition, concepts that we will explore in more detail.

THE NATURE OF "DISORDER" AND THE INTERPLAY OF FACTS AND VALUES

In the latter part of the 20th century, a group of thinkers, often referred to as neo-Kraepelinians, saw themselves as ending the dominance of psychoanalysis, countering the antipsychiatrists' critique, and re-orienting psychiatry into the mainstream medical tradition[14]. In doing so, they looked back to late 19th century European psychiatry, which became aligned with the rest of medicine when E. Kraepelin proposed an influential classification of mental diseases based on rigorous clinical description and natural history. Likewise, the neo-Kraepelinians claimed that precisely defined diagnostic criteria could be used to discover the specific biological causes of psychiatric syndromes and establish psychiatry as a branch of medicine[15,16].

Although the ideas of R. Spitzer, the architect of the DSM-III, differed in some respects from those of the neo-Kraepelinians, this approach helped to undergird the development of that diagnostic manual[17,18]. Furthermore, advances in psychopharmacology in the 1960s helped support a view that psychiatric disorders are discrete entities with specific pathophysiologies, and so respond differentially to medications. Indeed, D. Klein, a psychopharmacologist whose work influenced the development of the DSM-III, put forward the notion of "pharmacological dissection". He held that not only did mental disorders respond selectively to particular medications, but so did specific disorder subtypes. For instance, atypical depression responded preferentially to monoamine oxidase inhibitors[19,20].

In the 21st century, however, the relationship between the DSM and biological psychiatry has shifted, with biologically-oriented psychiatrists emerging as prominent critics of the manual. T. Insel, during his tenure as director of the US National Institute of Mental Health (NIMH), exemplified this shift. He emphasized that psychiatric disorders are brain circuit disorders, and that descriptive diagnoses based on symptoms rather than laboratory tests are not in alignment with the rest of medicine[21]. He also argued that, because the DSM categories are not biologically-based, the use of these categories in research interferes with rather than promoting the discovery of causal mechanisms of psychopathology. Hence Insel supported, in place of the Research Diagnostic Criteria (RDC) that were key to the development of the DSM[22], the development of a set of Research Domain Criteria (RDoC) by the NIMH[23], and foregrounded translational neuroscience as a foundation for psychiatry[21].

Indeed, it might seem that, over the course of its history, psychiatry has lurched from one model to another, in which entirely different concepts of mental disorder prevail. In the US, it is notable that psychoanalytic thought held sway for many decades, before giving way to a more neurobiological perspective[24]. There has also been considerable debate about the nature and classification of mental disorders, as perhaps most notably exemplified and spurred by the decision to exclude homosexuality as a disorder from the DSM[25,26]. In philosophy of science, T.S. Kuhn's notion of scientific paradigms has been enormously influential[27], and in psychiatry many have proposed paradigm shifts for the field[28].

The clash between different psychiatric models has brought conceptual conundrums to the fore. The notion put forward by both neo-Kraepelinians and translational neuroscientists that mental disorders are brain disorders, for example, raises a series of interrelated and perennial philosophical issues, including the validity of diagnostic concepts, the relationship between different explanations of mental illness, and the mind-body problem[29,30]. Each of these conceptual issues has important clinical and research implications, as exemplified in vociferous debates between proponents of biologically-oriented psychiatry vs. psychoanalysis, between those who emphasize intrinsic causes vs. social determinants of mental illness, or between supporters and critics of RDoC. Addressing these conceptual issues seems increasingly urgent, given the growing recognition of the burden of mental disorders, and the ongoing need for better interventions.

In this section we focus on the nature of mental disorders, providing a foundation from which to consider other key conceptual debates as the paper proceeds. The nature of mental disorders in turn raises a series of subsidiary questions, each of which will be addressed here: What justifies the position that a particular biological or behavioral state is a disorder? Do psychiatric classifications reflect natural features of psychopathology, or do they reflect our clinical and societal interests? Are mental disorders best considered as universal entities that are similar across individuals, or as shaped in particular ways that are unique for each person? What are the implications of psychiatric diagnosis for personal agency?

Disorder status: naturalism and normativism

In a straightforward binary version of this debate, naturalism and normativism are opposite and diametrically opposed views (see Table 1). The phrase "the disorder wars" comes to mind[31].

On one end lies *strong naturalism*, i.e. the view that the concept of "disorder" can be described in completely factual and value-free terms and can best be studied using methodologies continuous with those used in natural sciences such as chemistry and genetics. Many biological psychiatrists of the late 20th century held this view to the extent that they accepted that psychiatric disorders are caused by neurobiological dysfunction and understood abnormal psychology to be the result of objectively deviant brain functioning[15,16].

In the philosophy of medicine, the notion of disorder as objective deviation from a state of health is most notably expressed by C. Boorse. For him, health is a state of normal biological functioning, and functions are normal if they make a causal contribution to survival or reproduction that is typical for the species[32]. Boorse has been remarkably persistent in maintaining this view; twenty years after his original papers, he published a lengthy rebuttal to his critics[33], and nearly two decades later, at a symposium on his work, he again countered his critics[34]. Indeed, it has been suggest-

Table 1 Questions in the naturalist-normativist debate, and possible alternative responses

Are there biological and behavioral states that can be characterized as dysfunctional or malfunctional in objective terms independent of human interests?

- Yes, dysfunction can be described in entirely value-free terms.
- Dysfunction may not be explicitly defined in value-laden terms, but an evaluative component or human interests will play a role when the concept is operationalized in a particular context.
- No. There are biological and behavioral processes, but the characterization of these processes as "dysfunctional" is not an objective fact independent of human interests.

Is there an essence that is shared by all dysfunctions?

- Yes. The malfunctions are grouped together because they share an essence (e.g., they are all failures of a mechanism to perform a function for which it was naturally selected).
- No. Dysfunction refers to a family of related concepts, so that there is no one account of it that is uniquely correct or uniquely privileged, and there is no common characteristic that is shared by all. Some of these concepts may be value-free and others may be value-laden.
- Yes. What these processes have in common is a particular social or folk-psychological judgment of abnormality.

Is "dysfunction" necessary for disorder status?

- Yes
  - ○ Necessary and sufficient.
  - ○ Necessary but not sufficient – a harm component or a human-interest component is also necessary.
- No. Disorder judgments may be legitimately made in the absence of an explicit "dysfunction" judgment (e.g., based on considerations of biological or behavioral regularities – "mechanistic property clusters" – and harm).

What are the relevant human interests?

- Diverse considerations of harm (e.g., distress, disability, risk).
- Diverse clinical and scientific interests that arise in different contexts.
- Diverse stakeholders' interests and values.
- Sociocultural norms (social deviance).
- Functional norms of self-maintenance and adaptation.

ed that, after Boorse, philosophers of medicine must either work within his theory or explain why not[35].

On the other end of the divide, *strong normativism* holds that there is no natural, objectively describable set of biological processes that we can characterize as "dysfunctional", and hence disorder attributions are thoroughly value-laden. Normativists differ, however, on the presumed nature of these value judgments.

For K.W.M. Fulford, disorder is inherently normative because it is grounded in the "illness experience", the patient's direct experience of something having gone wrong, which is dependent upon social or folk-psychological intuitions of what is abnormal[36]. For Fulford, the value-ladenness of the illness experience not only unites medicine and psychiatry, but also humanizes both fields.

T. Szasz, renowned for his critique of psychiatry, provides an entirely different view. For him, disorder judgments in psychiatry are judgments of deviance based on sociocultural norms, with no evidence of the presence of a biological disease. His view of valid disorders arises from a strong naturalist view of physical disease together with a strong normativist view of mental illness. Diseases ought to be described in terms of objective pathological changes, and, as the states we call "mental disorders" are value-laden and without evidence of such alterations, their characterization as disorders or illnesses is a category error, a myth. For Szasz, value-ladenness becomes a reason to question the medical legitimacy of psychiatry.

It is crucial to appreciate, however, that those who view disorder concepts as inherently value-laden do not necessarily deny the biological reality of the afflictions. Naturalists and normativists may agree on the physiological and behavioral facts at hand and yet may disagree on whether the state in question is healthy or disordered[37]. As the philosopher R. Cooper has illustrated using a weeds and daisy metaphor, we can all agree on what a daisy is as a species, but disagree on its status as a weed[38]. Similarly, researchers can agree on the biological mechanisms of premenstrual dysphoric disorder, but disagree on its status as a mental disorder[39,40].

For naturalists, medicine is at its theoretical core a scientific discipline like other natural sciences and subject to a similar sort of interplay of natural facts and human interests[33]. For normativists, disorder concepts are not fundamentally scientific but rather are clinical and practical concepts. They are grounded in the experiences of distress, disability and disruption, which are interpreted to indicate that something has gone wrong and which lead patients to seek professional help for their problems. From a normativist perspective, medicine is at its core a practical activity aimed at reducing human suffering and enhancing well-being[36,41,42].

The naturalist-normativist debate acquires a particular valence in psychiatry in part because of the way value-ladenness has been wielded by antipsychiatry figures, such as Szasz, to challenge the notion of mental illness. New critical movements have gone even beyond this approach, by exploring how social and cultural values impact views of the normal and the pathological. Neurodiversity studies, for example, argue that cognitive profiles such as autism may be socially disabling, but are not intrinsically pathological[43,44]. Mad studies similarly resist the pathologizing of diversity and emphasize social factors as a cause of distress[45,46].

Binary positions have the advantage of being straightforward. However, one disadvantage is that, when they are understood in opposition to each other, their differences are often accentuated, such that each position may be defined by what the other rejects. Further, an important development in philosophy of science has been an appreciation of the role that values play in science and a recognition that the notion of value-free science is not only untenable but also undesirable[47]. For example, values influence which scientific problems are prioritized, how they are studied, how uncertainty is managed, how much evidence is considered sufficient, and how scientific evidence is used to inform practical decision-making. The incorporation of values and human interests into a broader notion of scientific objectivity has enriched our understanding of natural sciences.

Strong naturalism runs the risk of scientism, i.e. over-reliance on what is currently perceived as factual[48,49], while strong normativism runs the risk of a relativism where any socioculturally disvalued condition could potentially be considered a disorder. In philosophy, a position that has been termed "soft naturalism" attempts to avoid both scientism and relativism, and to acknowledge the importance of both facts and values in science[50]. Analogously, in philosophy of psychiatry, a number of different proposals have been put forward on how best to incorporate both naturalist and normative considerations in conceptualizing mental disorders[51].

A particularly influential integrative position, J. Wakefield's harmful dysfunction analysis, is a hybrid view that combines naturalism and normativism in roughly equal measures[52,53]. One component of disorder, "dysfunction", is defined in value-free, evolutionary terms. Dysfunction refers to the failure of biological or psychological mechanisms to perform the function which they were naturally selected to perform during evolution. The second component of disorder is that the dysfunction is harmful to the individual. Harmfulness is normative and, in Wakefield's view, largely determined by social standards. Wakefield has applied his harmful dysfunction analysis to a broad range of psychiatric disorders and, like Boorse, has engaged widely with critics over several decades[54].

According to Wakefield, for instance, developing depression in reaction to a stressor such as loss is an evolutionarily designed adaptive response to adversity and not a dysfunction. The DSM, therefore, makes an error by classifying such depressive reactions as disorders. It is only when depression occurs out of the blue, or does not resolve once the stressor is no longer active, or is accompanied by some specific features (such as suicidal ideation, psychosis, or psychomotor retardation), that it becomes reasonable for us to assume that mechanisms designed to regulate sadness in response to loss and adversity have failed[55,56].

One recent alternative to Wakefield's analysis is a hybrid account offered by J. Tsou. He defines mental disorders as biological kinds (value-free component) with harmful effects (normative component) and, by doing so, bypasses speculation about what normal psychological functions are products of natural selection[57]. Instead, drawing on the work of R. Boyd on clusters of properties in nature[58], he argues that valid biological kinds are those that exhibit characteristic regularities due to stable sets of interacting biological mechanisms, which allows us to make inferences and predictions about diagnostic categories. We can do this because the properties that define scientifically valid kinds are produced by similar sets of causal mechanisms.

For Tsou, schizophrenia is a disorder because it entails shared causal mechanisms that result in an identifiable cluster of properties with predictable regularities (i.e., it is a biological kind) and because it compromises the capacity of a person to function adequately as judged by sociocultural standards (i.e., it is harmful). However, Tsou would also include as disorders normal psychological reactions to stress, such as acute depression, which are characterized by biological mechanisms that fall in the normal range of function. Thus, the naturalistic standard of being a biological kind is broad enough to accommodate the range of conditions that mental health professionals treat.

Additional ways of bridging the naturalist-normativism divide have been proposed[59-64]. Gagné-Julien, for example, argues that judgments about dysfunction are value-laden but, provided that appropriate procedures are in place, they can be socially objective[64]. Nielsen and Ward argue that the key norm violation for disorders is a breakdown in the norms that support an individual's functioning within his/her social context[62]. They attempt to "naturalize normativity" by noting that, in the psychiatric domain, disorders entail cognitions and behaviors that run counter to an individual's self-maintenance and adaptation needs; disorder status is therefore based on the needs of the individual, rather than on societal norms.

Strong naturalism can be tempered by acknowledging that values and human interests play important roles in clinical and scientific contexts. Many would agree that the concept of disorder invokes value-laden notions such as disability, harm and suffering[65-67]. Authors such as L. Reznek, D. Murphy and R. Cooper consider disorders to be natural processes that are held together in virtue of human interests, akin to categories such as "weed" or "vermin"[38,68,69]. Such weaker forms of naturalist concepts of disorder may be seen as exemplars of a soft naturalism that emphasizes the complexity and fuzziness of the world, as well as the need to address both the mechanisms underlying disease and the experience of illness[70].

A view of science as influenced by values can also provide nuance to strong normativism. This can be tempered by appreciating that disorder characterizations often require negotiation between competing values, and arguing that the values which influence our definition of mental illness can be discussed and critiqued to reach a consensus on the type of values that are desirable in psychiatry (e.g., values concerning human flourishing, well-being, harm reduction, vs. oppressive values such as racism and sexism)[71,72]. Notably, Spitzer was open to articulating the values underpinning DSM-III[73]. Further, several authors have advocated for consultative decision-making processes that would include patients' voices on the question "What is a mental disorder?", in order to ensure that patients' interests are represented in psychiatric concepts and classifications[39,74-81].

Strong normativism can also be tempered by acknowledging that broad scientific agreement can be achieved on the co-occurrence and co-variation of signs and symptoms that characterize the psychiatric conditions regarded as disorders. For example, whether or not people have the symptoms of anorexia nervosa can be seen as an empirical matter, and the decline in functioning associated with these difficulties can be recognized by all observers regardless of the value-laden nature of the standards by which functioning may be judged to be impaired. Furthermore, scientific agreement can also be reached on the involvement of particular neurobiological processes in specific psychiatric conditions[82], even though these processes may not be characterized as "dysfunctional" on neuroscientific grounds alone[63].

Pragmatic considerations have assumed an increasingly prominent role in the conceptualization of mental disorders. Pragmatic accounts, however, tend to focus on clinical and scientific goals rather than sociocultural norms and values. For instance, in articulating the notion of a practical kind, P. Zachar argues that the development of disorder concepts in the DSM and the ICD can be seen as an attempt to calibrate concepts to multiple goals such as enhancing reliability, supporting etiopathological validity, facilitating communication, guiding treatment, minimizing stigmatization, and promoting research[83].

The bridging of the naturalist-normativist divide provides key lessons for clinicians. In particular, such bridging offers an important foundation for complementing evidence-based care with value-based care. Evidence-based care is largely focused on a synthesis of the medical literature, while values-based health care reminds us of the importance of assessing and addressing patients' values. Values-based care is consistent with a model of patient-centered practice, where the values of individual patients are central to evidence-based clinical decision-making. Fulford's model emphasizes that values-based health care is skills-based, with the most important skills being awareness (of values), reasoning and knowledge (about values), and communication skills[84]. Each of these skills draws on philosophical sources, but also exemplifies good psychiatric practice.

Psychiatric classification: tackling essentialism

Once we have implicitly or explicitly identified a class of mental disorders, a set of psychopathological states, or a community of psychiatric conditions/mental health problems, we can further ask: How do we map the territory of psychopathology? How do we distinguish between conditions within the class of mental disorders? How do we demarcate disorder from normality?

Philosophy of psychiatry has been helpful in clarifying the metaphysical and methodological assumptions that guide the search for answers to these questions. One common metaphysical assumption in psychiatric classification has been *essentialism*. This is the notion that categories have essences, identity-determining properties that all members have in common and that distinguish them from members of other categories. Kinds with essences have been called *natural kinds*, meaning that they reflect the structure of the natural world. In the context of psychopathology, an essentialist view implies that psychiatric disease entities are discovered through scientific inquiry, similar to the identification of infectious disease entities in medicine, and thus a valid psychiatric classification "carves nature at its joints", as Plato put it[85,86].

Philosophy of biology and of psychology have recently focused on how causal processes and mechanisms undergird observed phenomena[87-89]. When these processes and mechanisms are well understood, professionals are often able to use them as the basis for classification. This is the case for infectious diseases, in which classification based on identification of the causative pathogen is possible. However, when the processes and mechanisms of an illness are particularly complex, dimensional or multifactorial, knowledge of etiology by itself does not necessarily offer an optimal classification, and we rely on additional considerations – on what we want the classification to accomplish – to draw boundaries and set thresholds. This applies to many areas of medicine, but is an issue that is more pervasive and pronounced in psychiatry[90,91].

From a somewhat simplified metaphysical perspective, we may think of a classification as demarcating natural kinds, practical kinds, or social kinds. If psychiatric classifications such as the DSM and the ICD were demarcating natural kinds, we would expect each diagnosis to correspond to an entity that exists in the structure of the world, independent of human interests[85,86]. E. Kraepelin, for instance, believed in the existence of natural disease entities in psychiatry, and in addition held the view that pathological anatomy, etiology, and clinical symptomatology including course of illness, would all coincide in the case of such entities[92].

The assumption that there are natural disease entities in psychiatry was also adopted by the neo-Kraepelinians, and implicitly guided the development of the DSM-III[93,94]. Furthermore, the Kraepelinian notion of convergence of validators was also accepted by Robins and Guze[95], who assumed that their proposed validators of clinical description, laboratory findings, course of illness, and family studies would all point towards the same disease entities. This set the agenda for a research program for the next several decades in which researchers sought to validate the DSM diagnostic constructs.

By the 1990s, however, there was growing recognition that different validators might not inevitably align to offer a single privileged classification, in a way that amounts to a psychiatric version of the periodic table of elements[96]. Rather, different validators suggest alternative mappings of the space of psychopathology[97]. For example, in the study of schizophrenia, shared family history suggests a broad mapping (schizophrenia spectrum), whereas poor outcome indicates a narrower mapping (schizophrenia). In such a scenario, empirical facts alone do not determine which validators we ought to use. Our choice of validators depends also on our assumptions and goals, which may differ from practitioner to practitioner and from context to context.

In contrast to the natural kind view is the skeptical view that the categories of psychiatric classifications are social kinds, almost entirely constructed by social processes (i.e., strong social constructionism). This view appeals to many critics of psychiatry, who point towards the obvious influence of sociocultural factors on the presentation of psychiatric conditions, and the inability of psychiatric research to identify diagnostically valid biomarkers. The social kind perspective is further supported by examples such as "hysteria" and "multiple personality disorder", whose popularity among clinicians at various points in history has resembled the rise and fall of fashions. There is also increasing awareness that psychopathological phenomena are subject to "looping effects", such that the very act of classification modifies the behavior of the individual classified, further supporting the social constructionist view[98].

However, this view in its strong articulation seems untenable, as it fails to take into account that scientific research has discovered relationships between neurobiological processes and psychiatric symptom clusters, albeit these relationships do not necessarily correspond to specific DSM or ICD categories. For instance, psychiatric research has identified hundreds of genetic variations that are associated with a range of psychiatric disorders, so that genetic influences on psychopathology often cut across DSM diagnostic boundaries[99,100]. The relationship between genetic variants and psychopathology is therefore complex and transdiagnostic, but not absent or chaotic[101].

The notion of practical kinds offers a different contrast to the essentialist perspective on natural kinds, and aligns with the soft naturalist view that psychiatric science is both a scientific and social process. There may be no "natural joints" in psychopathology, but there are scientific facts in the form of symptom patterns and co-variation that constrain any scientific attempts at nosology[102]. Within these constraints, the boundaries that we draw will often reflect our pragmatic goals, and diagnostic thresholds will be influenced by both facts and values. Practical kinds are useful heuristic constructs that categorize the neurophysiological and psychological space in ways that serve our scientific and clinical goals. The pragmatic nature of psychiatric classification is also supported by considering the history of psychiatric nosology, which shows the contingent nature of our contemporary diagnostic constructs, and how our classifications would have looked quite different had certain key historical figures in psychiatry not existed or had they made different choices[103,104].

Distancing ourselves from essentialist assumptions about natural kinds in psychopathology allows us to appreciate the complexity of mental disorders, and makes it possible for us to map and model psychiatric phenomena using different approaches. For example, idiographic approaches focus on the uniqueness of the individual psychiatric patient – how his/her mental health problems arise from a specific combination of predisposing factors, developmental history, life experiences, behavioral adaptations, and psychological defense mechanisms. Such an approach utilizes broad principles of psychobiological functioning to formulate a narrative specific to a patient. The aim of classification, then, is to aid the development of a clinical formulation.

The failure to identify etiologically-based disease categories has also spurred psychometric efforts to model psychopathology. Psychometric analysis goes beyond manifest variables, which can be directly measured or observed, to mathematically model latent or hidden variables, which cannot be observed directly and only emerge through statistical analysis. This quantitative statistics research program is exemplified by the Hierarchical Taxonomy of Psychopathology (HiTOP) consortium[105]. This attempts to combine signs and symptoms of psychopathology into homogeneous traits, to assemble such traits into empirically-derived syndromes, and then to group these syndromes into spectra (e.g., "internalizing" and "externalizing")[106].

The psychometric approach of HiTOP has generated considerable debate[107-109]. First, in clinical practice there do seem to be some discrete entities, which respond to specific treatments; narcolepsy, for example, can be diagnosed using an accurate biomarker, and can be effectively managed using particular medications. Second, dimensions and categories are not necessarily mutually exclusive; for example, on the dimension of extraversion, a particular cut-point can be used to define an extrovert[110,111]. Third, of particular relevance to positions that emphasize the importance of causal mechanisms for classification, psychometric approaches emphasize descriptive features and may elide underlying etiology[61].

Another strand of philosophical inquiry has focused on the use of operational definitions employed by the DSM. In an effort to improve inter-rater reliability and to facilitate psychiatric research, the DSM from its third edition on has offered operationalized criteria for each disorder that specify details such as a list of (relatively specific) symptoms, number of symptoms that must be present, and the duration for which they must be present. How should the relationship between the criteria and the disorder be conceptualized? Lack of clarity in this regard leads to another form of confusion, in which operational criteria are thought to constitute the disorder itself.

Operational definitions are partial definitions that do not specify all the details of the phenomena being studied[112]. They have an element of vagueness that becomes evident when new scientific questions force us to articulate concepts with greater precision. The DSM excluded non-specific symptoms (such as anxiety in depression) from operational criteria, but these symptoms as still part of the syndrome being described (e.g., depression). Moreover, the polythetic nature of DSM criteria allows for many different symptom configurations to meet disorder threshold, but these different symptom configurations are not seen to constitute different disorders. Instead, they are better understood as different ways in which we can identify a disorder.

K.S. Kendler has elaborated on the distinction between diagnostic criteria as indexical and constitutive[113]. When diagnostic criteria are regarded as indexical, they are understood to be fallible ways to identify a disorder; when they are regarded as constitutive, the symptom criteria *are* the disorder. According to Kendler, the DSM criteria are intended to be indexical, and viewing them as constitutive is a conceptual error. Thus, for example, there are 227 ways to meet DSM criteria for major depression, but these are different ways of indexing major depression, not 227 types of major depression[114]. There is no single and privileged correct operationalization; rather, different operational definitions can be refined and optimized for different purposes.

Taken together, an emerging contemporary view of psychiatric taxonomy incorporates the dimensionality of psychopathology (there are few discrete entities), insights from complex dynamic systems (relatively stable symptom patterns can emerge from irreducible interactions between multiple factors), and perspectives from embodied cognition (causal mechanisms traverse the brain, body and environment). Such a view of psychopathology does not render categorical diagnostic systems such as the DSM and the ICD invalid or useless, but it encourages us to give up an essentialist bias that has led us to reify them – to attribute them a correspondence to objective reality that they do not possess[115,116].

How is this view of taxonomy relevant to clinical practice? Clinicians need to be aware of the work that has gone into, and the value of our nosology, while also being mindful of its tentative nature and significant limitations[117]. In particular, although the DSM has clinical utility, it has often been criticized for facilitating a checkbox approach to psychiatric assessment and evaluation. Clinicians ought to be aware that important features of mental disorders may well have been described in the psychiatric literature, and yet may not be listed in the DSM[118]. Further, while diagnosis may begin with the DSM or the ICD, a comprehensive evaluation needs to assess a range of domains, including clinical subtypes, symptom severity and staging, cognitive schemas, environmental stressors, and protective factors[119]. Finally, clinical formulations need to supplement our growing knowledge of the characteristics of psychiatric disorders with an idiographic understanding of each individual patient[120].

Psychiatric diagnosis and personal agency

Debates concerning psychiatric taxonomy may have important implications for individual self-conception and self-understanding[121]. As noted, the DSM criteria should not be taken literally as being fully constitutive of disorders, but they are nevertheless often taken as such, and the influence of the DSM on how mental disorders are perceived has been profound. Concern has been raised about the undue extent of this influence, especially given the inevitable neglect of person- and context-specific factors in diagnostic criteria[121].

More broadly, debates about the nature and classification of disorders are also implicated in the effort of patients to understand the boundaries of their selves in relation to their disorders. Given that both psychiatric conditions and psychiatric medications can affect deep aspects of self-experience (such as perceptions, desires and feelings), ambiguity and uncertainty can arise with regard to where the "self" begins and ends, and how the self is impacted (or compromised) by both illness and treatment[122,123]. The experience of ambiguity at the phenomenological level can be further compounded when patients are "confronted with the vagueness and uncertainty associated with the issue of 'what *is* a psychiatric disorder'"[123].

Questions concerning the interplay of agency and mental disorders have also been central to debates concerning the relevance of these disorders to assessments of moral responsibility. While psychopathology has often been treated as paradigmatically exempting or mitigating in the literature on moral responsibility, there has been a growing shift to more nuanced assessments and an increasing emphasis on the need for case-by-case evaluation[124]. These trends reflect the larger recognition of person-specific and situation-specific factors that affect the manifestation of psychopathology in any particular individual. In many cases, the relevant agential capacities are diminished or deeply compromised, but nevertheless present. In addiction, for example, it is often implausible to speak of blanket incapacitation, given that aspects of choice and deliberation are often involved. A useful body of philosophical work has explored the question of responsibility in the context of mental disorder[125-127].

More broadly, the question arises of how different ways of conceptualizing psychiatric disorders influence our attitudes towards affected individuals. While it was presumed that more biological conceptions of disorders would reduce stigmatizing attitudes in general, empirical research points to far more complex interactions[128]. These findings align with theoretical concerns regarding the interpersonal and social costs of perceived diminished agency, which, while sometimes decreasing perceived responsibility, might simultaneously increase other forms of aversion. Indeed, empirical research has suggested that in some contexts biological conceptions may ultimately be more stigmatizing for affected individuals[129].

The awareness of the impact of psychiatric diagnoses on the self-conception and self-understanding of those diagnosed has supported the view that people with lived experience might usefully contribute to the development of psychiatric classifications. They may be better situated to assess the impact of changing diagnostic criteria on access to care or the potential risk of stigma associated with certain nomenclature issues, or be better able to identify mismatch between diagnostic criteria and subjective experiences[39,74-81].

The clinical implications of different conceptual approaches to personal agency and moral responsibility have been debated by philosophers, and this area deserves further attention and research[125,126].

PLURALISM IN PSYCHIATRY

In philosophy of science, Kuhn's notions of dominant scientific paradigms that are incommensurable, and of revolutionary shifts in such paradigms[27], have become very influential. Arguably psychiatry provides a useful exemplar of how different paradigms dominate over the course of time. In fact, critics of psychiatry have argued that the replacement of one psychiatric paradigm by another may entail neither scientific progress nor clinical advancement[130,131].

At the same time, Kuhn has been criticized for his relativism[132]. After all, scientific models can be reasonably compared, and there may be justifiable grounds for replacing one model with another. In psychiatry, although there have certainly been important shifts in theoretical frameworks, it might also be argued that current clinical research and practice incorporate valid aspects of both psychodynamic and neurobiological approaches, as well as concepts and data from a range of other models of psychopathology. Different models may be able to engage usefully, as evidenced by the emergence of neuro-psychoanalysis, or by work on how psychotherapy impacts on neuroimaging. Psychiatry has arguably advanced precisely by incremental integration of a range of valid models[28].

Psychopathology seems to involve multiple causes, and it is possible that different psychiatric models shed light on different causes. Philosophers, starting from Aristotle, have long emphasized the importance of multi-causality in both biology and pathology[1,133]. Behavioral scientists have similarly emphasized the need to explicate different kinds of causes of behavior and psychopathology[134,135]. Jaspers, a philosopher-psychiatrist well known for distinguishing between knowledge of causal explanations and understanding of meaningful connections[3], can be regarded as a methodological pluralist, with his pluralism influencing a range of subsequent authors in philosophy of psychiatry[136].

In contemporary philosophy of science, there is an ongoing debate about whether and how diverse explanations can be integrated[137]. In the 1970s, G. Engel, an American internist who had experience working with psychosomatic disorders, argued that the dominant model of disease was biomedical, thus neglecting the psychological and social dimensions of illness[138]. He therefore proposed a biopsychosocial model, aiming for a framework that could be used in research, teaching and clinical care. Clearly, it is important that we avoid both a brainless psychiatry and a mindless psychiatry[139], steering clear of both scientism and culturalism (which are overly reductionist about science and culture respectively)[49,140].

However, the biopsychosocial model has also received stinging criticism for being overly eclectic and non-specific[141], and for offering no particular framework to conceptualize multi-level causal interactions[142] or allow optimal selection of causal mechanisms[143]. Further, its practical use in psychiatric formulation has led to an inadvertent reification of "biological", "psychological" and "social" as distinct ontological domains[144]. Ongoing efforts to understand the nature of causal explanations in science in general[145,146], and in psychiatry in particular[147,148], remain therefore crucial.

An explicit emphasis on pluralism is a relatively recent development in philosophy of science[149]. Unsurprisingly, for philosophers who regard it as important, there is not a single unified approach to pluralism. Instead, from the time of Aristotle, through the work of early American pragmatists[150,151], and on to contemporary philosophers[152,153], a number of different pluralisms have been delineated and developed. We next consider three important notions of pluralism – *ontological pluralism, explanatory pluralism, and value pluralism* – as well as some of their clinical implications.

Different notions of pluralism

The first notion to consider is *ontological pluralism*. As noted earlier, the notion of natural kinds reflects the possibility that nature can be carved up in an objective way to form discrete entities[85,154]. Exemplars of such natural kinds are often found in physics or chemistry; the periodic table of elements is a particularly compelling one. Ontological pluralists have, however, argued that there are different ways of dividing reality, reflecting different scientific interests and values, and that a range of different classifications may be valid. From the time of Aristotle, pluralists have often looked to biology. Species can certainly be divided on the basis of their evolutionary history, but there are also alternative ways of classifying organisms[155,156].

Our earlier discussion emphasized that mental disorders are not simply natural kinds that emerge from empirical investigation. At the same time, our constructs of mental disorders are not merely conventional. Instead, they are rigorously informed by scientific research, including work on a range of different validators, which reflect the involvement of a range of different underlying structures and mechanisms. They may be regarded as "soft natural kinds"; although they cannot simply be discovered by carving nature at its joints, and although our classifications and descriptions are value-laden, these entities nevertheless incorporate an accumulating scientific appreciation of psychobiological structures, processes and mechanisms[157].

The notion of "soft natural kinds" may be useful in the clinic in a number of ways. Consider the construct of "behavioral addiction". From a neo-Kraepelinian perspective, the lumping of substance use disorders together with gaming and gambling disorders suggests that these conditions have overlapping phenotypic features, and share key validators, such as clinical course. In fact, however, the situation may be much "fuzzier": the psychobiology of alcohol dependence is likely to differ significantly from that of gambling disorder, given that alcohol has direct toxic effects on the brain. However, a key rationale for lumping these conditions may instead be a public health perspective[158].

Consider also the boundaries between disorder and normality[159]. Current versions of the DSM and the ICD appropriately emphasize that the boundary between disorder and normality is not hard and fast, but rather can be fuzzy and indeterminate. In some other areas of medicine, biomarkers can be helpful in making the clinical decision as to whether a disorder should be diagnosed, but this is not the case in psychiatry. Critics of psychiatry may conclude that mental disorders are entirely a matter of convention, and that psychiatric diagnosis is merely a matter of "labelling". However, this ignores the complex reality of mental signs and symptoms: psychiatric phenotypes are not elements in a periodic table but rather are comprised of overlapping dimensions, and thresholds for disorder reflect a range of considerations[160].

The second notion to consider is *explanatory pluralism*. Philosophers have emphasized that science employs multiple partial models. Indeed, the model or metaphor of maps may be useful in describing such pluralism; a cartographer may employ multiple different maps of the world, each accounting for different features of reality, and each of which is useful for a particular purpose. As noted earlier, in philosophy of psychiatry there is ongoing debate about the extent to which the biopsychosocial model, which encourages a focus on different dimensions of disease and illness, is merely eclectic, or provides the appropriate scaffolding for considering a range of causal mechanisms.

A major area of debate in philosophy of science regards reductive explanations. It has long been argued that the phenomena of the world can be organized along different levels, ranging from the physical through the biological and on to the social. A reductionist approach aspires to explain higher level theories (e.g., biological models) in terms of lower level accounts (e.g., physical models). Certainly, as science has progressed, such inter-theoretic reduction seems to have occurred; thus we can account for the properties of DNA (which plays such a key role in biology) in terms of its particular structure (that is, in terms of its underlying physicochemical properties)[161,162].

Pluralists have emphasized, however, that such successes are only part of the story of science. Science is often concerned with phenomena that emerge only at higher levels of organization: these require models that cannot simply be reduced to lower level accounts[163-165]. Furthermore, as emphasized in the metaphor of science as cartography, multiple different sorts of models of reality may be useful for different purposes. Focusing on biological science, S. Mitchell concluded: "Given the multiplicity of causal paths and historical contingency of biological phenomena, the type of integration that can occur... will itself be piecemeal and local... Pluralism with respect to models can and should coexist with integration in the generation of explanations of complex and varied biological phenomena"[166].

Discussions of pluralism often refer to the relationships between different "levels" of explanation, but "levels" themselves are better understood as ways of referring to different sorts of organizational (part-whole), spatial and temporal relationships[167]. Slow vs. fast and large vs. small might carve things up differently than higher vs. lower, so that a pluralist approach to explanation is required[167]. In philosophy of science and neuroscience, there is an ongoing exploration of how best to conceptualize causal processes and mechanisms, including causality across different levels[168-171]. For psychiatry, however, it is key to be aware of the complexity of psychobiological systems, and to avoid overly simplistic neuro-reductionism[75,172,173].

Once again, these philosophical constructs have practical import. Psychiatric practice and research ought to involve a broad range of disciplines and methodologies. Applying scientific pluralism to psychiatry, Kendler has argued that first-person subjective experiences and sociocultural factors play a vital role in the etiology of psychiatric disorders, such that this etiology cannot be captured by just focusing on the basic biology of the brain[174]. He suggests that a pluralistic psychiatry should aim for "patchy reductionism" and "piecemeal integration" as it tries to understand the multi-level causal interactions that give rise to psychopathology [174].

When we think about psychotropic medications, for example, we often focus on specific receptor effects. While important, this downplays how these agents exert a cascade of effects, impacting neural networks and ultimately behavior. A pluralistic clinical psychopharmacology is needed in order to flesh out these higher-level mechanisms in greater detail. Further, complex multilevel explanations involving a range of mediating processes are needed to explain higher-level phenomena such as placebo and nocebo effects, and to account for molecular-social interactions such as how antidepressants acting on serotonergic pathways may impact social hierarchy. While the focus of much psychopharmacology has been on lower-level mechanisms, such as receptor actions, a pluralistic approach emphasizes that cognitive and phenomenological processes can also be important psychopharmacological targets[175]. Analogously, a pluralistic approach may be useful in exploring the causes of change during psychotherapy[176], and in developing integrative models of psychotherapy[177,178].

The third notion to consider is *value pluralism*. This notion, which emphasizes that there are many different moral values, is typically considered as a position in moral philosophy. However, value pluralism is also relevant to science in general, and psychiatry in particular, in a number of ways. In particular, choices about how best to classify and describe the structures and mechanisms of the world reflect a range of epistemic values, and indeed debates about scientific pluralism intersect with debates about science and society[137]. Differences between the DSM-5 and the ICD-11, for example, do not necessarily reflect scientific disagreement, but rather acknowledgment of differences in their most important aims and associated values[179].

Additionally, the argument that natural kinds reflect clusters of properties has been extended to value-laden constructs. "Healthiness", for example, may reflect a range of related features, presumably underpinned by relevant biological processes[180]. However, if we think back to normativist positions on the definition of mental disorder, which emphasize the influence of social and cultural values, different societies and cultures may have different understandings of mental disorder because they value different conceptions of human flourishing[42].

Philosophical work on value pluralism has long emphasized that, given the plurality of values, choices between them will be complex. The philosopher I. Berlin emphasized that different values may be incompatible, and this seems consistent with our experience of moral decision-making[181]. Nevertheless, this does not necessarily mean that value-laden choices cannot be made in a reasonable way. Aristotle emphasized the importance of practical wisdom, arguing that a virtuous person succeeds in making correct choices[182]. While practical wisdom may in part involve the application of general principles, Aristotle emphasized the "priority of the particular" in choosing the correct course of action[183].

Value pluralism again has a number of clinical implications. As noted earlier, the psychiatrist-philosopher K.W.M. Fulford and his colleagues have argued that evidence-based health care needs to be complemented by value-based health care[184]. A growing literature on shared decision-making similarly highlights the important perspectives of those with lived experience of mental illness[185,186]. Furthermore, value pluralism emphasizes the importance of a range of epistemic virtues, including epistemic and cultural humility[187].

Conceptual tools for psychiatric explanation: beyond reductionism

Three important and interrelated concepts may be useful for psychiatric explanation: *dynamical constitution, downward causality*, and *dual aspectivity*[188-191]. They are employed in several recent pluralistic approaches, and are important aspects of the embodied approach explored later.

Dynamical constitution is the notion that objects and processes at smaller scales of enquiry can interact over time in ways that produce objects, systems or processes at larger scales of enquiry, and that qualities of the larger objects can emerge from the interaction between the component objects and processes[188,190]. *Downward causality* is the idea that these emerging objects, systems and processes at larger scales of inquiry can entrain, constrain or otherwise have causal influence over objects at smaller scales. *Dual aspectivity* refers to the idea that, whenever talking about a living system, there are at least two perspectives that one can take: first, a body-as-object, naturalistic or third-person perspective; second, a body-as-subject, personalistic or first-person perspective. Both perspectives consider the same physical object, but they capture different aspects of the living system/person under study, in line with a pluralist approach[189,192].

Taken together, these concepts provide an approach to understand constitutionally complex systems such as life forms. Organisms are made up of many parts (e.g., organs, cells, receptors) and derive properties, such as mindedness, from the complex interactions between these parts in context. Both the parts and the wider organism are no less real because of the knowledge that we gain about the parts and how they manage to dynamically constitute a minded creature. Analysis at multiple scales of enquiry – consistent with an emphasis on a complex systems framework and a pluralist approach – is useful for understanding how this creature functions and how things may go awry.

From a clinical perspective, these considerations emphasize the complexity of clinical formulation and intervention. Given dynamical constitution, neurobiological mechanisms are key to shaping behavior, thoughts and emotion. However, given downward causality, such mechanisms cannot be assumed to have causal primacy in our explanations. In contrast to the view of neo-Kraepelinians and overly reductionistic translational neuroscience, mental disorders are not merely brain disorders[29,30]. Conversely, interventions such as psychotherapy may impact both brain and mind[193].

The biopsychosocial model remains the most influential for ensuring a pluralistic approach to assessment and intervention for mental disorders in the clinical context. Despite criticisms that highlight its shortcomings, including the absence of an explanatory account of causal interactions, this model remains valuable because it prompts us to resist simplistic binaries – such as the organic vs. functional, biological vs. psychological, medical vs. social, and disease vs. behavior distinctions – in our explanations of psychiatric etiology[194,195], and serves as a powerful reminder that a pluralistic framework which considers a broad range of "difference-makers" is needed in clinical research and practice[75,117,148].

Jaspers' insistence that both explanations of underlying mechanisms and understanding of individual meanings are important for a comprehensive account of mental disorders remains relevant to contemporary clinical practice. Medical anthropologists have usefully distinguished between disease as a biomedical condition, and illness as the subjective experience of those suffering from that condition[196]. Relatedly, work on what has been termed "neurophenomenology" attempts to integrate neuroscientific knowledge with individual experience[192,197]. Finally, "explanation-aided understanding" – the idea that knowledge of causal mechanisms can enhance our appreciation of first-person experience – is also a key consideration for improving clinical practice[198].

EMBODIED COGNITION AS A PLAUSIBLE INTEGRATIVE APPROACH

The "mind-body problem" is a paradigmatic issue at the intersection of psychiatry and philosophy. The philosopher R. Descartes is often cited for his substance *dualism* – that mind and body exist as radically different kinds of substances – and clinicians are typically encouraged to avoid this position in light of a modern naturalist or scientific understanding. At the same time, clinicians are generally not encouraged in their training to explore recent developments in an area of such philosophical complexity, and as a result some implausible assumptions can arise[199].

One commonly assumed view is that the mind is a powerless or "supervenient" side effect of the physical processes of the brain. Such a view can support neurocentric assumptions, for example, within a biological psychiatry which contends that the brain is where we need to focus the vast majority of our explanatory and treatment efforts. As noted earlier, while the brain is clearly important for understanding mental functioning and mental health, such an approach may be criticized for its neuro-reductionism, where minimal space is made for similarly important aspects of human functioning such as experience, meaning, culture and context.

Another common view, inspired by the development of computers, is to see the mind as a "software" running on the "hardware" of the brain. Under such a *computationalist* and *functionalist* view, cognitive functioning is understood as a form of information processing where the brain takes sensory input and computes appropriate responses. Such an assumption can be seen in the notions of cognitive biases and core beliefs in cognitive-behavioral therapy, with these biases or beliefs effectively performing the role of "bugs in the software" altering our perception of the veridical world. While this can be a useful metaphor, there are multiple issues with this perspective. It is difficult to see how such a view can be integrated with a biological perspective, in which neurons and behaviors are complexly intertwined. Indeed, such a view seems implausible; living creatures are not computers with set functions, and this analogy may limit our insight.

Moving beyond assumptions of supervenience and computationalism, *embodied cognition* represents a biologically plausible and strongly integrative view of the mind-body relationship, whereby factors across the biopsychosocial spectrum are considered to have potential explanatory value[144]. Such an embodied perspective has gained momentum within philosophy of psychiatry in recent years, but is not yet broadly recognized by clinicians nor discussed in training programs. Engagement with embodied understandings of the connection between mind and body is a key development in philosophy of psychiatry.

Applied to psychopathology, notions of *embodiment*, alongside related ideas such as *embedment, extension* and *enactivism*, which we will soon unpack, represent one plausible integrative frame for the study and treatment of mental disorders. We argue that an embodied approach has the potential to incorporate and build on many of the recent conceptual developments highlighted in previous sections, while also cohering well with other contemporary theoretical and methodological developments in a range of disciplines. In this section, we first define some key terms and review the development of embodied cognition. We then go on to discuss the application of this approach to the study and treatment of mental disorders.

What is embodied cognition?

Embodied cognition refers to a diverse range of approaches across multiple disciplines within cognitive science, including but not limited to psychology, neuroscience, philosophy, robotics, and artificial intelligence. Embodied cognitive science is united by a common interest in moving away from a "cognitivist" or "computationalist" view, where the brain is seen as an isolated "seat of cognition" that receives sensory information, represents the world, and computes appropriate responses to it. Instead, embodied approaches variously emphasize the role of the body and context both in the moment-to-moment constitution of cognition and in the shaping of cognition across development, thus decentering the ideas of representation in how we seek to understand the mind[200]. Instead of understanding the mind through implicit analogy to computers, embodied approaches seek to understand it through analogy to complex living systems adapting to the dynamics of their environment.

Historically, the development of embodied cognition has many roots. The most commonly recognized of these roots include: a rejection of a traditional symbolic-representational view of cognition where the experienced world is a model/representation of reality; an interest in expanding upon the success of minimally representational "connectionist" understandings of cognition such as exemplified by neural networks; the emphasis of pragmatic philosophers such as J. Dewey on how knowledge entails interaction with the world; phenomenological insights by authors such as M. Merleau-Ponty that the body is an intrinsic part of our experience-of and engagement-with the world; work in developmental psychology by J. Piaget and others who have emphasized interaction with the world over time; and inspiration from the success of dynamic systems theory in modelling the behavior of complex systems[201]. Such historical antecedents have converged to produce understandings of the mind that recognize a broad range of influences shaping human cognition, from genes and molecules to culture and context.

Embodied cognitive science is a diverse field. This is true to the point that the very word "embodied" can take on subtly different and overlapping meanings in different contexts. It is therefore important to specify the sense in which we use this term. In a summary review of embodied cognition, Shapiro and Spaulding highlight three different yet overlapping themes within the various usages of the term "embodied". They refer to these three different themes of overlapping meaning as *constitution*, *conceptualization* and *replacement*[202]. In this paper, we generally refer to the *constitutional* understanding of embodiment. It is, however, worth briefly explaining all three senses of the term.

In the *replacement* sense of "embodied", emphasis is on the need to replace our systems of understanding the mind with less representational and more dynamical ones. In other words, developing ways of understanding the brain, not as generating a mirror-like representation of the world, but rather as resonating with the world directly. A classic example would concern how best to think about the action of catching a fly ball in baseball. Rather than representing the entire environment and computing the ball's trajectory, a non-representational and embodied view would suggest that we engage with simple visual strategies in order to ensure that we are in an optimal position to catch it[203]. This sense of embodiment is particularly associated with the position of "radically enactive cognition", which attempts to understand cognitive processes with no reference to representation[204].

When the term "embodied" is used in a *conceptualization* sense, the focus is on psychological concepts and processes, and how they are shaped by the kinds of bodies and experiences we have. The key idea is that the way we conceptualize the world would likely be different if we had different sorts of bodies to navigate with. For example, consider the idea that we think in terms of "up" as metaphorically connected to positivity and action, and "down" as connected to depression and inaction, not simply as a cultural quirk but because of shared associations rooted in our bodily experiences and actions[205]. Accumulating behavioral and neurobiological evidence supports the related ideas that: a) there is significant overlap in the neural processes involved in sensorimotor coordination and those involved in so-called "higher" cognitive and social processing, and b) such overlap means that "higher" cognitive processes are not siloed in the brain, but are influenced by bodily and sensorimotor context such as posture, current action, and internal physiological state[206,207].

When used in a *constitutional* sense, which is our main focus here, "embodied" refers to the idea that mental processes are best thought of as not constituted by the brain alone, but rather as emerging from the brain and body acting in concert, i.e., as one extended system. The mind does not arise from the efforts of the brain to represent the world, but rather is an active process of the entire organism navigating, adapting to, and making sense of the world[197,205,208-211]. In such a view, for example, the release of cortisol and adrenaline from the adrenal glands in response to an acute stressor is not simply an event occurring at one level of analysis with a modulating effect on cognition at a higher level of analysis, but rather is *part of* a single, body-involving, cognitive-affective response to threat. Thus, the processes that constitute emotions weave in and out of the brain, and include a range of interoceptive components[207,212]. This sense of embodiment incorporates the ideas of dynamical constitution, downward causality and dual aspectivity, discussed earlier.

Now that we have outlined what is meant by *embodiment*, it is useful to define some related ideas, specifically those of *embedment*, *extension* and *enactivism*. Together these ideas, alongside embodiment, are often discussed under the umbrella term "4E". Sometimes "5E" is also used, typically in reference to a focus on emotion.

Embedment is the idea that cognitive functioning involves a constant interplay with the environment across multiple timescales. Consequently, in order to understand cognition, recognition of the role of context is vital. When considering human functioning, the environment is also regarded not simply to be a physical one, but a social-cultural one, constituted by others, alongside their artifacts and shared structures of meaning[213]. Embedment highlights that, across the timescales of evolutionary change, sociocultural development, life-span learning, and moment-to-moment cognition, human beings are both deeply influenced by, and in turn influence, their surrounding environments. Even the most abstract and intellectual activities, such as mathematics, entail a thoroughly embodied and embedded skill set[192,205].

Extension is an idea in many ways similar to embedment, but which makes a more radical claim. Specifically, it is the idea that cognitive processes are often best understood as extending out beyond the body and looping through the world[213]. To continue the mathematics example, rather than merely understanding a calculator as supporting the cognitive processes of an individual, an extended view of mind would hold that the calculator becomes part of the cognitive process. In a well-known thought-experiment, Clark and Chalmers contrast Inga, who navigates from memory, with Otto, who has Alzheimer's disease and relies on written directions in a notebook. Given that the only difference between the two cases is that the process of navigation takes place wholly inside the brain in Inga's case and partly outside it in Otto's, they argue that it is arbitrary to limit cognition to what occurs within the confines of the skull[214].

Enactivism is an idea that subsumes and builds upon those of embodiment and embedment. It may be explained in different ways and with different points of emphasis, but here we focus on *autopoietic enactivism*[215]. "Autopoietic" simply means "self-creating". Accordingly, within autopoietic enactivism, the focus is on the notion that mindedness is brought forth, or rather enacted, through the organizational structure of life forms and their efforts to constantly maintain themselves within the context of their environment. An enactive perspective holds that life forms are shaped through evolution to try to survive, and that this inherent purpose sets up the necessary groundwork for the emergence of relational *meaning*. In order to survive, organisms have to learn how to seek food, avoid predators, and so on – that is, to respond differentially to affordances in the world[216]. Cognition is *sense-making* – a constantly unfolding process, one that involves body and action, is relational, and is inherently affective/meaning-laden. Thus, cognition is not a linear process of sensation-perception-cognition-action, but rather a circular process of sensory-motor engagement. The brain, rather than taking in information and representing a model of the world, as in the neurocentric view, is instead an organ of coordination, learning and mediation within this sensorimotor loop, so allowing for more complex ways of making sense of and acting in the world[189,217].

Overall, the embodied/4E model of cognition presents a non-dualistic understanding of the mind that appears biologically plausible and does not fall prey to reductionistic temptation. Human functioning is understood from this perspective in a way that preserves a sense of agency, while also recognizing the diverse array of influences that shape and influence human health and behavior, from genes to culture. It is therefore an integrative view, demanding both current and historical analysis of the entire brain-body-environment system if we are to understand patterns in human behavior and cognition. This approach is consistent with a coordinated pluralism[218], and arguably even with an integrative pluralism[219], and has led to the suggestion that accounts of mental disorder grounded in embodied/4E cognition may represent a path to solving the "integration problem" in psychiatry; i.e., the fact that we have identified causal factors across the brain, body and environment, but struggle to conceptualize how these causes come together to shape patterns of disorder[220].

Clinical applications of embodied/4E cognition

Several conceptual frameworks grounded in the embodied/4E perspective have been applied to mental disorders as a whole[189,191,220,221]. These frameworks view mental disorders as representing *disruptions to sense-making*, a view that is consistent with attempts to bridge the naturalist-normativist divide, with an emphasis on the adaptive fit between individual and context that aligns with soft naturalism[62,222]. They also share a vision that embodied/4E cognition serves as an integrative framework for the conceptualization, study and treatment of these conditions, consistent with an emphasis on multi-disciplinary and pluralist approaches. Additionally, there have been several efforts to develop descriptive and explanatory models of particular mental disorders from an embodied/4E perspective[223-228].

A focus on embodied cognition leads to a view of mental disorders as *constitutionally complex*, involving biological, cognitive-emotional, environmental and sociocultural aspects. This perspective emphasizes both *biology* and *agency*, acknowledging biological scales of enquiry as relevant without reducing the explanatory importance of experience and choice. It also incorporates ideas of dynamical constitution and downward causality to break down the received mind-body divide, and aligns well with the notion of mental disorders as fuzzy mechanistic property clusters[229].

Through the notion of embedment, these frameworks emphasize the active and historical role of the physical and sociocultural environment. All organisms, particularly humans, are deeply historical and ecologically informed creatures. Shaped by our evolutionary, sociocultural and developmental pasts, we are understood to strive to adapt to the present context and predicted future[207,212]. Applied to psychiatry, this allows integration with perspectives such as evolutionary psychiatry[230], cultural psychiatry[196,231], and developmental psychopathology[232].

In the embedded view, however, culture is not seen only as a historical force having influence across development, but also as a living context. In this "constitutional view", culture is seen as a "shared world" or structure of knowledge, meaning and artifact, constituted by ongoing engagement[212]. Such a shared world represents a historical context for the development of individuals and the way they make sense of the world, but also continues to play out in the moment-to-moment interaction of individuals, including in the clinical encounter. Embeddedness therefore pushes clinicians to actively consider the role of culture in the lives and histories of their patients, and in the clinician-patient interaction.

Via the notion of enactivism, these frameworks subscribe to a *process orientation*, with mental disorders not viewed as static problems/dysfunctions in the brain or psyche, but rather as constantly unfolding patterns of how we make sense of and engage with the world. Through interactions with their specific environment and its particular affordances, thinking beings create and discover meaning for themselves. Rather than stemming from some underlying "cognitive error" or "psychic disturbance", mental disorders emerge within the circular relationships between patient and world – as a maladaptive pattern of sense-making[191].

This process orientation accords well with the focus of neuroscience and computational psychiatry on *active inference*, whereby predictive processing frameworks formally model how organisms develop probabilistic assessments of their environment so as to adapt optimally. Indeed, several authors have considered how best to integrate such frameworks with embodied/4E approaches, noting that the brain-mind, including interoceptive components, engages in embodied predictive processing in order to maintain enactive engagement with the environment[206,233,234]. In their embodied/4E account, Friston and colleagues suggest the term *enactive inference*[235]. Their framework bridges representational and non-representational approaches[236], providing a pluralistic, yet formal and mechanistic, account of a range of psychiatric conditions, often with a particular focus on interoception and bodily states[237,238].

In the clinical setting, given the central role of affordances and affectivity within the enactive view, a process orientation accords with psychotherapies that draw patients' attention to early maladaptive schemas and current emotional dynamics in order to better learn to navigate them[239,240] – an exercise in sense-making about sense-making[191]. Further, from the enactive perspective, therapeutic interventions in psychiatry seek to improve the fit between the individual and his/her environment. This can in turn be achieved either by altering the sense-making and behavior of the individual, or by changing the world around him/her. This entails integration with notions of social psychiatry and environmentally focused mental health interventions.

One instructive example of the clinical utility of an embodied/4E perspective is the work of Tschacher and colleagues on schizophrenia[225]. These authors point out that sensorimotor dysfunctions are closely associated with psychotic symptoms, leading to altered timing in the processing of stimuli and to disordered appraisals of the environment. They argue, therefore, that problems of social cognition can be viewed as disordered embodied communication. Finally, on the basis of this account, they suggest novel treatment strategies through body-oriented interventions. Again, an embodied/4E approach is theoretically able to integrate biological and phenomenological perspectives, and also has practical implications for the clinical context.

As a final clinical example, consider an embodied/4E approach to addiction[227]. Addiction is embodied insofar as the impact of substances on neurobiological mechanisms alters mental activity, the body itself is altered in unhealthy and use-supportive ways, and habitual actions play important roles in substance-related behavior. Addiction is embedded/extended insofar as addiction-related behavior is both influenced by and often alters the environments within which it unfolds, and is shaped by individual learning histories. Finally, addiction is enacted insofar as an affected person's experience of and engagement with the world is deeply altered in a way that often works against his/her values, and the person enacts a particular and inflexible way of trying to meet his/her needs. In this framework, a merely neural model is replaced by a view of addiction as simultaneously neuronally-and-externally constituted, and there is an account of how drug-taking transforms the world of the individual – altering his/her personal agency and lived experience.

There are several advantages of such a view. First, this perspective allows an integration of neurobiological accounts of addiction with accounts of lived experience. Second, the binary choice of seeing addiction as a medical disease vs. a personal choice – a key issue in the philosophy of this condition[241,242] – can be seen to be an overly simplistic false dichotomy. Third, this perspective enables us to reconsider strategies for recovery; in particular, it provides an account of how the person with addiction may be able to change his/her lived experience by manipulating the environment and altering its affordances – so that there is a change in the dynamic interaction of brain biology, interoception, and surrounding context.

DISCUSSION

Psychiatry is, inherently, a conceptually laden and conceptually complex field. Yet the opportunity to reflect on the concepts implicit in psychiatric practice arises infrequently for both clinicians and trainees. Instead, a range of tacit assumptions – about the nature of mental disorders, diagnostic categories, causal explanations, and the mind – influence daily engagements with psychiatric taxonomy, clinical assessment and diagnosis, and the discussion of conditions and treatments with patients. These tacit assumptions have, however, been carefully addressed by philosophy of psychiatry, and here we have reviewed key advances in this field and their clinical implications.

In conceptualizing and categorizing mental disorder, both naturalist and normativist considerations have emerged as important – the field increasingly accepts that such work entails a consideration of both facts and values. At a conceptual level, this encourages moving away from strict scientism to soft naturalism – a position that embraces both psychobiological mechanisms and personal agency. In clinical practice, the bridging of naturalism and normativism facilitates moving away from an approach in which disorders are reified, and towards appropriately comprehensive and individualized evaluations of patients. Awareness of the importance of facts as well as values can also facilitate a mental health care that is both evidence-based and values-based.

In considering the nature of psychiatric science, there is now increasing emphasis on a pluralist approach, including ontological, explanatory and value pluralism. Conceptually, this acknowledges the multi-level causal interactions that give rise to psychopathology, and is consonant with Jaspers' early pluralist approach, encompassing both explanatory accounts of behavior and an understanding of the individual person – an approach espoused by a wide range of philosophers[50]. Clinically, this view emphasizes the importance of a broad range of causal "difference-makers" as well as considerations of "lived experience" in both research and practice.

In addressing a range of questions about the brain-mind, and how both somatic and psychic factors are key in mental disorders, conceptual and empirical work on embodied cognition provides an increasingly valuable approach. Viewing the brain-mind as embodied, embedded and enactive facilitates the integration of advances in both cognitive-affective neuroscience and phenomenological psychopathology, as well as in a range of other disciplines. Work on embodied cognition is having an increasing impact on rethinking mental health and mental disorders[189,191,220,221].

Conceptual competence has various elements, including making explicit conceptual assumptions, developing a philosophical vocabulary, acquiring familiarity with relevant frameworks, and maintaining a degree of "conceptual humility"[7]. These elements have been exemplified in this paper, but at this point we would like to emphasize in particular the virtue of epistemic humility. For example, philosophy of nosology has taught us that, despite the enormous amount of work that has been done to improve our classifications, these remain tentative, and reification of putative entities must be strenuously avoided.

Similar considerations would apply to our attempts here to advance philosophy of psychiatry. We began by noting that progress in philosophy has been disputed, and we are wary of claiming too much. Some of the issues in philosophy of psychiatry date back to ancient times, and some of the constructs employed seem to be "essentially contested": there are a range of competing views, and there deserves to be ongoing discussion and debate[243]. This applies in particular to the concept of disease, which may be intractably messy [31,244]. Still, the purpose of philosophy is not necessarily to resolve every dispute or to eradicate disagreement, but rather to properly articulate and understand debated issues. To the extent that the issues considered here have been more rigorously articulated in theoretical work, and more thoughtfully considered in the clinical context, some progress may be claimed.

Several limitations of the approach taken here deserve particular emphasis. First, we have summarized arguments and conclusions from the literature, rather than attempting to rigorously defend any particular stance. Relatedly, we have not had space to address ongoing work and key variants of some positions that have been put forward here, nor important critiques of these positions[50,245-248]. Key constructs employed here – including soft naturalism, pluralism, and embodied cognition – all deserve much deeper consideration.

Second, while we have drawn some links between these particular constructs – soft naturalism, pluralism, and embodied cognition – our view is that much further work along these lines is possible. At the broadest level, some work on these constructs seems to allow for a degree of rapprochement between analytic and continental philosophy[249]. At a more specific level, it seems to us that further linkages can be made between key philosophers who have spoken to these issues (including J. Dewey – who prefigured notions of embodied cognition[250], W. Sellars – who contrasted the scientific and manifest image[251], and H. Putnam – who contributed to work on collapsing the fact/value distinction[252]), as well as between work on cognitive-affective neuroscience and phenomenological psychopathology[192,253].

Third, we have been selective in our focus on progress in the field, omitting large swaths of work in philosophy of psychiatry – not the least being ethics (which will be the topic of another forthcoming Forum in this journal) – and potentially downplaying a range of authors and advances. Similarly, we have not covered the philosophy of any particular psychiatric symptom or disorder in detail, despite a large literature addressing a range of mental conditions. The breadth and depth of work by both ancient and modern philosophers who have considered the questions raised in this paper is extraordinary, and we would encourage readers to explore further.

An important meta-question is the extent to which there has been work on the cognitive science of philosophy and psychiatry. An embodied cognition perspective suggests, for instance, that, when we think about categories such as mental disorders, rather than being aware of how deeply reliant we are on the use of embodied metaphors, we are instead prone to essentialize our concepts[60,254]. We may therefore have particular difficulty in avoiding the traps of reductionism and reification, and in articulating and working with fuzzy constructs such as the bridging of naturalism and normativism.

A number of key themes have emerged from the different parts of this paper. Here we highlight three. First, a key theme has been that of integration. We have discussed the integration of elements of naturalism and normativism, of evidence-based care with values-based care, of knowledge of science with the understanding of experience, and of psychobiological mechanisms with personal agency. Further, we have emphasized the potential value of the embodied/4E approach in integrating a range of disciplines concerned with the brain-mind, including cognitive-affective neuroscience, developmental psychopathology, and social psychiatry.

A related theme has been that of "balance". Our notions of mental disorders need to avoid the poles of scientism and relativism; our explanations need to avoid both neuro-reductionism and culturalism; and our approach to the mind-brain problem should be one that avoids both a brainless and a mindless psychiatry[139]. Our introduction mentioned Aristotle's notion of the "golden mean", and the emphasis in Chinese philosophy on the balance of *yin* and *yang*; a balanced perspective that is able to judiciously weigh up a range of principles and particulars surely lies at the heart of good clinical work[255].

A final theme has been that of complexity. We have argued that it is important to avoid essentialism and reductionism in psychiatry, and that clinical assessments need to go far beyond our diagnostic criteria to assess a range of domains, and to understand each patient as a unique individual. While monocausal models of disease entities (e.g., *Treponema pallidum* causing neurosyphilis) have been useful, contemporary psychiatry requires a coordinated[218] or integrative pluralism. The embodied/4E perspective emphasizes the complexity of the living being's dynamic engagement with his/her environments over time. The complexity of the brain-mind and of clinical conditions is a key reason why calls for simplistic paradigm shifts in psychiatry are unlikely to succeed. Instead, in keeping with philosophy as the love of wisdom, there is a need for a "wise psychiatry".

The philosophical resources reviewed here may be useful in considering the extent to which psychiatry has made progress in the past, our current balance of success and failure, and our future aspirations. It seems to us incontrovertible that philosophy has played a key role in psychiatry, whether implicitly or explicitly, and that it will continue to do so into the future. Our immediate hope is that work in philosophy of psychiatry will contribute to the conceptual competence of clinicians. By rendering the implicit explicit, philosophical analysis may help expose the implications, limitations, contradictions and even absurdities that potentially underlie received ideas and prominent positions. Our long-term hope is that advances in philosophy of psychiatry will in turn have positive clinical impact, contributing to integration, balance and wisdom in psychiatric practice.

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DOI:10.1002/wps.21194

Five conceptual competences in psychiatry

Stein et al[1] survey a range of recent developments in philosophy of psychiatry that are relevant to clinicians. They recommend that clinical training include the development of "conceptual competences", i.e. philosophical skills and theoretical frameworks that bring new intellectual resources into psychiatry[2]. Here I would like to elaborate on the conceptual competences that Stein et al mention, discuss how they have grown in the last 30-40 years, and add a further one to their account.

Perhaps the most important conceptual competence is *conceptual humility*, i.e. the awareness of the partial and provisional nature of current psychiatric knowledge. This brings an expectation of what I have called (in the more general context of medical knowledge as a whole) "messy pluralism"[3]. Our theoretical grasp of psychiatric phenomena is through a variety of intellectual frameworks with loosely demarcated scopes. These frameworks may lead in productive directions, or be wrong in ways that we do not know how to anticipate, or lead to unexpected consequences that we will need to investigate and refine. Proceeding with conceptual humility means accepting pluralism, rather than forcing a premature choice between partial truths, as well as treating contradictions generated by multiple different frameworks with curiosity rather than epistemic horror.

A second conceptual competence is *going beyond dualism*. For much of the 20th century, several psychiatric questions have been approached from either a "scientific" (such as that of neuroscience) or a "humanistic" (such as that of phenomenology) perspective. K. Jaspers' *General Psychopathology*[4] is a typical example of this kind of dualism, as is P. Kramer's two ways of approaching clinical cases in *Listening to Prozac*[5]. These approaches sometimes compete in providing different accounts of the causes of psychiatric conditions, with neuroscientific accounts eschewing "cognitive penetrability" in favor of mechanistic causes, and phenomenological accounts aiming, sometimes dubiously, for narrative completeness. Such dualism is a simple example of "messy pluralism", involving two approaches. P. Kramer shows skill in making use of both perspectives in handling particular cases. What is called for now is an expanded ability to juggle *more than these two* perspectives, i.e. a more complex and nuanced pluralism. The common bifurcation into scientific and humanistic approaches is a misleading oversimplification of the theoretical options, which include a variety of scientific, humanistic and mixed approaches. Hence, going "beyond dualism" is an important conceptual competence.

A third important conceptual competence is the appreciation that psychiatric concepts often aim to achieve *a variety of goals* in addition to traditional scientific ones such as descriptive accuracy, predictive success, and explanatory power. Psychiatric concepts are expected to identify appropriate subgroups for specific treatments, underlie appropriate guidelines for social/educational/legal eligibilities, provide categories for clinical research, support intuitions about moral responsibility, and sometimes even supply social identities. Proposed concepts can be rejected or modified because they are thought to be inaccurate, or too difficult to apply reliably, or problematically stigmatizing to some patient groups. One of the enduring lessons of the DSM process is that no single system of concepts can satisfy all such goals at all times. There are inevitable trade-offs between different important goals. Stein et al refer to this in terms of an "interplay of natural facts and human interests". Zachar[6] has introduced the idea of "practical kinds" as a supplement to "natural kinds". A good example of responsiveness to different goals is the shifting way in which intense and prolonged grief symptoms have been handled from DSM-III through DSM-5-TR, trying to strike a balance between effectively addressing human suffering and avoiding "pathologization" of normal reactions to loss.

A fourth important conceptual competence is an awareness of which groups, individuals, professions etc. *control the discourse* of psychiatry. By "control the discourse" I mean the mixture of earned and unearned authority that shapes how new ideas are received from the public, patients, families, and various health care professionals. The DSM era – from 1980 until recently – has been marked by the powerful control of the American Psychiatric Association, in which group consensus of experts, led by psychiatrists with some participation from psychologists, provided grounds for accepted categories and concepts. Recently, there have been multiple calls for a more democratic social epistemic process, especially one that includes "experts by experience" (traditionally called "patients")[7]. As of 2023, the DSM process itself is still conservative, allowing the input of experts by experience only during the stage of public comment on proposals.

A final useful conceptual competence that I would like to add to Stein et al's suggestions is what I will call *hembig awareness*, taking the neologism "hembig" from Alvesson and Blom[8]. Writing in the academic field of organization studies, they find that the handling of some key concepts (such as "leadership", "strategy", "institution") is central and important, but confusingly imprecise and ambiguous. A "hembig" concept is one that is hegemonic (plays a regulatory role), ambiguous and big (wide and often unclear in scope). It is important to be aware of which concepts are hembig, so that problematic ambiguities and inferences can be avoided. The main hembig in psychiatry is the term "psychiatric disorder", which is a metaphor (the literal – but not the actual – meaning of "disorder" is "lack of order").

While there have been attempts to define "psychiatric disorder" technically, using necessary and sufficient conditions, these attempts have generally fallen short of their intended generality. They have included "maladaptive patterns of sense making" (K. Nielsen), "harmful dysfunction" (J. Wakefield), harmful biological kinds (J. Tsou), predictive failures in Bayesian processing (A. Clark, K. Friston), socially deviant judgments (T. Szatz), "madness as strategy" (J. Garson), and box canyon (local minimum) solutions in cognitive processing (K. Kendler). L. Wittgenstein's alternative suggestion that theoretical terms such as "psychiatric disorder" mark "family resemblances"[9] has been a helpful meta-metaphor

– but still only a metaphor – for starting to explore how these kinds of concepts work.

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DOI:10.1002/wps.21195

Professionals in psychiatry need reflective competence

The paper by Stein et al[1] provides a comprehensive and timely overview of key theoretical advances in work on philosophy and psychiatry. The authors respond to the grand epistemological questions of psychiatry – the classification debate, the nature of psychiatry, and the mind-body problem – with soft naturalism, pluralism, and 4E cognition, respectively. Though I empathically comply with their considerations, I was surprised by the self-centered view of psychiatry. The authors see psychiatry as a scientific and clinical island in splendid isolation without relationship to society in which it is embedded. Here I address a perspective that takes in account: a) how psychiatry is shaped by forces of society; b) how the above-mentioned topics are influenced by philosophical assumptions held by the global community; and c) why the concept of conceptual competence, in agreement with Stein et al, is indispensable for professionals in psychiatry.

Psychiatry is not a stand-alone discipline. It dialogues continuously with other sciences such as pharmacology, neuroscience and psychology. In fact, except for descriptive clinical phenomenology, which has been largely neglected lately, innovation often takes place outside psychiatry, through development of new drugs, new techniques in imaging and genetics, or psychotherapeutic restyling. Artificial intelligence predicts that in the near future substantial innovations in psychiatry may be expected in psychedelic-assisted therapy, neuromodulation (repetitive transcranial magnetic stimulation and deep brain stimulation), and digital personalized psychiatry.

On closer inspection, we should even recognize that psychiatry, more than any other medical discipline, is being determined not by science but by society. All psychiatric symptoms are ultimately defined on the background of what is commonly agreed upon as normality. Normality is established not by science but by society. Normal is individual behavior that conforms to the most common behavior. Fluctuations in prevalence of mental disorder across culture and time are not caused by sophisticated adaptations of scientific criteria by experts, but pushed by societal waves. Autism and attention-deficit/hyperactivity disorder have become 100-fold more common due to changing perspectives on education and productivity. Long before misophonia became known in psychiatry and sporadically entered scientific articles, the disease term circulated globally on the Internet between interest groups. Often psychiatry is lagging behind social developments. Only in 1974 did homosexuality disappear as a disorder from the DSM-II, and only in 2019 did conditions related to sexual identity disappear as mental disorders from the ICD-11.

We should accept that psychiatry no longer shapes itself. The course and faith of psychiatry is not determined by psychiatrists or philosophers, but by socio-economic variations fueled by influencers on social media. The current and ongoing identity crisis in psychiatry is due to the yet-to-be-embedded realization that psychiatry as a scientific discipline has lost control of itself, sadly popularized by the universal theme of mental well-being.

Normality has profoundly changed. Whereas for a long time "mental health" was the norm, now "mental well-being" is paramount. Every self-respecting institution, from companies to universities, appoints "well-being officers". Mental health refers to the absence of mental illness. Mental well-being refers to the presence of favorable conditions, including experiencing positive emotions, maintaining relationships, and feeling meaningful in life. Mental well-being includes feeling good in your own skin, being resilient and able to enjoy life. In view of the "norm" of mental well-being, every person has become a potential patient.

Mental disorders are reported to be highly prevalent. Around 1-in-7 people have one or more mental disorders. In 2020, rates of depression and anxiety have climbed globally by more than 25%. This increased rate of mental disorders is not due to changes of perspectives in psychiatry, but of social processes reflecting philosophical values. Once you are born in this world, you are expected to actualize yourself as an individual autonomous person, i.e. an absolute authentic and perfectly self-determining subject. We are all brought up with the assumption that individual freedom is the highest attainable thing in life. The Western ideal of human being is the autonomous person who thrives best in the greatest freedom, surrounded by the greatest convenience, and striving for absolute self-determination and maximum self-actualization. Each step towards greater individual autonomy takes us higher up the evolutionary ladder, further away from the animal instinct.

The Western ideal of unlimited autonomy has been globalized in line with consumerism and technologism. Unfortunately, most people fail to comply with that ideal. First, the ideal is either unattainable or untenable. Second, the constant bombardment with social commands to self-maximize, to become ourselves, and to prove that we are worth it, makes people feel stressed, exhausted, traumatized, burn-out, lonely, useless and meaningless. Third, though people suffer because they cannot meet the high demands of a society that values the absolute ideal of individual autonomy, this society does not allow mental suffering. Failure is no option. Individual autonomy dictates that we need to be successful; that we are always in control and feel happy. Since mental suffering is unacceptable, mental distress is allowed only as a psychiatric disorder for which we carry no individual responsibility and are not to blame.

Mental disorders are not spiking because more patients are developing psychiatric diseases, but because the ideal of individual autonomy has become the standard of normality across the globe. It is no coincidence that anxiety and depression are the most common mental disorders. They express our failure in attempting to fulfil the impossible demand of individual autonomy. We are more anxious not because our world has become more dangerous – on the contrary it has become safer – but because our desire for control is out of proportion. We are more depressed not because our lives are hopeless and meaningless – the opposite is actually true – but because we are confronted with too many choices, we are set up for unrealistically high expectations, and blame ourselves for any and all failures.

I was delighted to read about "conceptual competence" in Stein et al's paper. I want to go one step further. The competence of a psychiatrist should include three different skills: *professional competence*, or the theoretical knowledge and training to practice your profession; e*xperiential competence*, or the clinical expertise through years of contact with patients or clients; and *reflective competence*, or the ability to reflect on your profession, the specific role you hold in it, and how they are affected by society.

Reflective competence is the transformative awareness of how conceptual assumptions in society shape clinical care. The philosophical presuppositions of health and illness, mind and body, normal and abnormal are constantly changing in a globalized and digital world. Imperceptibly, they determine the validity of diagnosis and treatment. That is why thinking about our profession is part of the basic skills of every professional. Just as a jeweler not only designs jewelry but also calculates gold prices, a psychiatrist takes into account society's view of mental suffering in addition to what emerges from his/her contact with patients.

Following the crisis in psychiatry, colleagues called for "a fundamental rethinking of the creation and training of psychiatric knowledge"[2]. A survey found that 65.2% of mental health professionals struggle with conceptual and philosophical questions related to their profession, and only 4.3% feel that training adequately prepared them to face this intellectual challenge[3]. Is it the task of psychiatry to reflect, beyond psychopathology of individuals, about philosophical values of modern societies? But, then again, do we have a choice?

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DOI:10.1002/wps.21196

Philosophy of psychiatry can gain greater vitality by engaging the implications of new science

Stein et al[1] introduce philosophy of psychiatry by presenting a series of well-curated, historically grounded positions on topics with which the discipline has been centrally engaged. These include the definition and boundaries of psychopathology, the unsettled nature of diagnostic constructs in psychiatry (including the dialectic between naturalism and normativism), the perils of essentialism, and mind-brain relationships. They introduce these topics partly through the compelling device of asynchronous "conversational" threads containing positions and arguments from successive writers, and accompany this exposition with their own gently reflective comments. They also provide intellectual frameworks to orient readers who are coming to these topics for the first time. For example, they offer a context within which to understand the debate between naturalist and normativist positions on the definitions of psychiatric disorders, a debate that might be less familiar to readers coming from scientifically more mature fields of medicine that confidently ground diagnoses on knowledge of etiology and pathophysiology[2].

Stein et al compare strong versions of naturalism in psychiatry, which hold that disorders can be defined in purely factual, value-free scientific terms, with strong versions of normativism, which hold that disorder definitions always require value judgments, and which in their most extreme form devolve into the relativism exploited by the antipsychiatry movement of the mid-late 20th century. They then discuss compromise or bridging positions – epistemically more defensible and pragmatically more useful than either extreme. Unfortunately, in defending compromise, the authors seem satisfied with "soft naturalism", a concept that is too amorphous to set useful conceptual structures for a much needed future nosology that successfully captures disorders with diverse etiologies and pathophysiologies, ranging from monogenic neurodevelopmental disorders associated with autism to highly polygenic disorders with significant developmental and environmental etiological factors, such as depression and post-traumatic stress disorder, for which there are no bright line boundaries with health.

Indeed, it is treacherous to consider psychiatric disorders (e.g., all disorders included in the DSM-5) as a natural grouping that can be conceptually encompassed by any single definition or generalization. What is contained in the DSM-5 list of mental disorders is historically contingent, based in part on phenotypic similarities, in part on ignorance of etiology and neural mechanisms, and importantly on disciplinary claims and practice patterns that – as illustrated by movement of disorders among chapters in the ICD-11 – may be contested by other disciplines, such as neurology, sex endocrinology or pediatrics[2,3].

Philosophy is a highly abstract discipline when focused on basic principles such as being, knowing, causality, and basic justifications for ethical principles. In contrast, as well illustrated by Stein et al, philosophy of psychiatry is concerned with applications of philosophical tools to the complex brew of theories, cognitive schemata (including disease classifications), hypotheses, empirical observations, policies and practices of a particular medical discipline. Philosophy of psychiatry gains traction on issues of importance to its diverse stakeholders through its interdisciplinary stance, with one foot in basic philosophical concepts and analytical methods, and the other firmly planted in the theoretical constructs, practices and science that undergird the discipline. In this context, the paper by Stein et al is especially timely, because the scientific basis of psychiatry is evolving rapidly and is already changing some corners of practice and policy – developments that will clearly benefit from philosophical analyses.

During the last two decades, significant advances in technology and computation (including machine learning and data science) have not only opened new scientific possibilities, but have also motivated significant changes in the organization of biomedical science, such as the creation of international data-sharing consortia (e.g., the Psychiatric Genomics Consortium[4]) and large deeply phenotyped and genome sequenced populations cohorts (e.g., UK Biobank). Psychiatric research has exploited these developments to produce remarkable advances in genetics[4]; progress in relevant aspects of molecular neuroscience, connectomics and cognitive neuroscience; and powerful new approaches to phenotyping and epidemiology based on electronic medical records, large recontactable cohorts, and data sciences.

Only fifteen years ago there were zero replicable genetic associations with psychiatric disorders. Today there are hundreds, and a few examples of integrated genetic and neurobiological data have already yielded candidate mechanisms for schizophrenia and other illnesses[5]. Such mechanistic hypotheses are in turn informing new rational discovery efforts for biomarkers and therapeutic targets. In the translational realm, connectomics and machine learning have produced circuit-based therapies (such as open- and closed-loop deep brain stimulation) that are already in clinical trials or in clinical use[6].

Growing evidence for brains as "prediction machines", emerging from cognitive and systems neuroscience, makes a strong case that brains construct subjective experience and behavior from Bayesian priors corrected by interoceptive and exteroceptive sensory information. If such understandings of brain function continue to gain evidentiary and conceptual support, as I believe they will, ideas about brain-mind relationships, sense of self, personal identity, and agency – so central to philosophy and psychiatry – will require substantial revision. In terms of mental illness, a Bayesian brain model can provide useful new ways for thinking about conditions as diverse as addiction, hallucinations and delusions[7], and the mechanisms by which cognitive-behavioral psychotherapies exert beneficial effects. All of these scientific developments have profound philosophical implications not only for the classical problems of philosophy of psychiatry, but also for a range of issues ranging from the concept of self to volitional control of behavior.

Modern genetics and neuroscience provide much information that should influence modern attempts to define psychopathology or classify psychiatric disorders. Human genetics demonstrates that DNA sequence variants associated with psychiatric disorders ("risk alleles") are continuously distributed in populations, without any break or inflection point that would naturally demarcate a categorical separation from health[2]. Epidemiological studies also demonstrate the continuous distribution in the population of symptoms and impairments associated with major depressive disorder and other common psychiatric conditions. In addition, individual risk alleles act pleiotropically, influencing multiple disorders. For example, schizophrenia and bipolar disorder share approximately 70% of their common variant risk alleles. For disorders that have been studied, unbiased single cell analyses of gene expression (from sequencing RNA) and epigenomics (from patterns of chromatin accessibility) performed in post-mortem brains find only quantitative differences between affected and unaffected individuals, and much overlap in gene expression between the disorders.

These findings impugn the setting of categorical boundaries between DSM disorders, and strongly favor transdiagnostic dimensional definitions. Moreover, significant "within disorder" heterogeneity of underlying mechanisms confounds clinical research, contributing to the failure of attempts, through structural and functional imaging, to robustly and reliably distinguish cases from controls. Thus, current categorical disorder definitions not only impose artificial boundaries between named disorders, but also fail to yield homogeneity within putative categories.

One additional discovery deserves emphasis here: at the genetic as well as the phenotypic level, diagnosed disorders do not exclusively represent deficits. For example, obsessive-compulsive disorder, polygenic autism, and anorexia nervosa share alleles with beneficial phenotypes, such as greater educational attainment and, in the case of autism, greater cognitive ability[8,9]. Overall, a significant number of DNA variants associated with impairing symptoms may also be associated with strengths that have opposite valences with respect to life success and survival. Such scientific observations certainly complicate, if they do not defeat entirely, attempts of commentators to claim that psychiatric disorder definitions can be based on their speculative inferences about natural selection.

Psychiatry is entering a time of significant change in its underlying science, that is just starting to influence the clinic[6] and to gain the attention of policy makers. This is a time in which the analyses and reflections of philosophy of psychiatry should gain in importance, driven by engagement with new science. Stein et al have done an important service in providing a lucid platform from which psychiatry can better address its future.

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DOI:10.1002/wps.21197

Launching the social philosophy of psychiatry

Stein et al[1] provide a state-of-the-art summary of the philosophy-psychiatry field that centers around the mind-brain-world triumvirate. They do an astounding job summarizing 30 years of activity in the field, culminating in a present-into-the-future consideration of embodied cognition.

Here I look forward in a different direction. Borrowing the internalist/externalist distinction from historiography, externalist philosophy of psychiatry might be paraphrased as a social philosophy of psychiatry. Externalist philosophy of psychiatry would consider the role of the social and cultural world in shaping conceptions of mental illness and its treatments. It would consider social phenomena as environmental contributors to the complex causalities that converge on psychopathological phenomena. It would reconsider concepts of free will in terms of structural features of the human organism alongside the structural features of our increasingly complex social environment. It would draw upon philosophy of technology, social epistemology, metaphysics, political philosophy, and philosophical anthropology in placing clinical diagnosis, research and theory into sociocultural contexts. Through understanding these social contexts, we can find new clarity in the mental health project.

I can make these abstract generalizations more vivid by considering some examples from our current, and rapidly changing, era. I mention very briefly three areas ripe for development by social philosophers of psychiatry: the engulfment of clinical activity by electronic medical records; the role of domination by the State in mental health; and the psychopathology of artificial intelligence (AI).

Back in 1977, Heidegger[2] introduced the concept of "enframing" to the then-developing philosophies of technology. "Enframing" involves the tendency of technologies to appropriate resources for their own purposes, forming a "standing reserve" of resources increasingly remote from human goals. Heidegger's thinking helped to found the now-familiar philosophy of technology tropes such as "technologies solve problems which in turn generate new problems, requiring new technological solutions". This recursive expansion of technological imperatives can be seen playing out in clinics around the world through electronic medical records. Psychiatric training directors are already noting the deterioration of interviewing and diagnostic skills when young trainees are driven to checking box after box of clinical findings, being "enframed" into the metaphysical structure of those records, and missing the big narrative picture of the patient. What made "enframing" toxic for Heidegger was that technologies change the way we think, as in the above-mentioned check-box interviews. Fortunately, philosophers of technology have been working on this set of problems for a while, and philosophers of psychiatry can find a rich literature. The response to digital "enframing" has already begun[e.g.,3].

The archeologist/anthropologist team of D. Graeber and D. Wengrow[4] reconsider world history with a particular interest in the origin of social inequity and the origin of the State (e.g., government). As social scientists, they have access to and can interpret archeological and anthropological sciences freed from the limits of written text "traces". By studying cultural artifacts, they can provide evidence about the diversity of community living over the millennia. One of their major insights is the common threads that constitute domination of people by other people – e.g., social control. They identify three factors that are apparent singly, doubly or triply in virtually all the cultural forms of dominated communities: control of violence, control of knowledge, and control by charisma. *Control of violence* refers to the people who are authorized to apply violence to others, whether war-making or managing crime (as just two examples). *Control of knowledge* has to do with the people controlling what counts as truth and knowledge. *Control by charisma* has to do with the persuasiveness of the would-be empowered group; the ability to bring believers/followers into the fold.

The authors note that the most successful domination occurs when all three factors of the triad are seized. They also note that the means to capturing the three factors are not determinative; one can have democratic, imperial or fascist dominations, for example. I need not detail the relevance of these concepts to our current world situation, but I can point to their relevance to the social philosophy of psychiatry. We have seen the rise of populist authoritarian rule over the past decade – the *charisma* element. We have witnessed the loss of confidence in "elites" – scientists, professors, philosophers, intellectuals and doctors. More importantly, talk of "post-truth" and the transformation of public lying from vice to virtue is eroding our prior forms of the domination of *knowledge*. Control of *violence* is also being shaken worldwide, as social media enable the challenging of conventional mechanisms of violence control (policing, the courts, civil liberties, rule of law, subordination) through familiar tropes such as #Icantbreathe, #metoo, and the unprecedented January 6 storming of the US Capitol building. For philosophers of psychiatry, the range of tasks deriving from these social changes is huge. Some are simple to conceive: how do clinicians communicate around these phenomena? Others are definitional: how many people must believe something before a false belief is not a delusion? Still others are insidious: what counts as mental health in a post-truth world where confidence in State institutions is diminishing?

In recent months we have witnessed the explosion of AI technology proffered by the major info-tech companies. We have also witnessed gushing enthusiasm as well as apocalyptic worries from many users and commentators. Somewhere in-between these social reactions resides the systematic appraisal of these systems as they evolve. We have seen how human biases are entrained in AI, leading to perpetuation of bias in later use[5]. We have also seen both absurd and frightening results of natural language devices when asked ordinary questions[6]. Social philosophers of psychiatry can envision the development of looping effects of human-AI deviant interchanges online and worry about the social consequences. Some examples of inquiries in this area point to treating deviant AI responses as psychopathology analogues[7]. Others consider using AI tech as explanatory models of human psychopathologies and tools for therapeutic developments[8]. We can also envision the engagement of AI into disputes about medical and other misinformation in the social media environment, thus connecting psychopathology of AI to social-domination theory described above. Some preliminaries of this work have appealed to a "father" of philosophy of psychiatry: K. Jaspers[9].

All this potential work is wide open, deep and important.

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DOI:10.1002/wps.21200

Another "and": philosophy as glue

Offering a timely perspective on contemporary philosophy of psychiatry, Stein et al's paper[1] is part-review and part-pitch for an integrative model of the mind, "embodied/4E". As such, the paper nicely captures the collegiality that is a defining feature of the field. Blossoming across the world in the 1990s, the renaissance in philosophy of psychiatry has largely avoided the tribal schisms by which so many "psy" disciplines have been marred. Indeed, Stein et al adopt an integrative stance: the dominant connective throughout is "and" ("Western *and* Eastern" philosophies, "facts *and* values"); "philosophy *of* psychiatry" itself is used interchangeably with "philosophy *and* psychiatry"; there is a helpful discussion of the varieties of pluralism; and "embodied/4E" is presented not as a panacea but as a model for integration (mind *and* body, normativism *and* naturalism, and so forth).

The Swiss historian and psychiatrist P. Hoff has characterized the history of psychiatry as one of serial collapses into single message mythologies[2]. After all, "binary positions", as Stein et al note, "have the advantage of being straightforward". That philosophy of psychiatry is avoiding factional splitting is thus a particular strength. Yet, this brings with it vulnerabilities. Which is why another "and" should be added. To the many varieties of expertise-by-training celebrated in this paper, we should add the expertise-by-experience of patients and carers.

To be clear, Stein et al emphasize the importance of what they call, variously, "lived experience", "subjective experience", "individual experience" and "first-person experience". But what is perhaps worth highlighting is the growing significance of co-production between experts-by-training and experts-by-experience in clinical work, in research, and in philosophy of psychiatry, both internally and for its wider significance across mental health care as a whole. Here, I comment briefly on each of these areas.

The significance of co-production in clinical contexts derives from recovery-oriented practice, i.e. practice aimed at recovering a good quality of life as defined by the values of – that is, by what matters or is important to – the *individual concerned*[3]. So defined, the criteria of recovery, in any given case, are necessarily derived from the expertise-by-experience of the individual in question. Expertise-by-training of course remains important, *inter alia*, to advising on the evidence-based interventions supporting recovery, to interpreting the values defining recovery where (as in anorexia nervosa) these are empathically obscure, and to balancing conflicting values (as in compulsory treatment). The clinical importance of expertise-by-experience is thus not at the expense of expertise-by-training. To the contrary, both are needed. The requirement for co-production is, again, conjunctive not disjunctive. But the point is that, without expertise-by-experience, recovery-oriented practice cannot even get started.

Similar considerations apply to research in the neurosciences, though in this instance with the importance of co-production for translation in mind. A notable challenge for psychiatry is that psychiatric scientists themselves have become increasingly critical of the persistently low rates of translation of neuroscientific research into improvements in clinical care: the architects of DSM-5 and its critics[e.g.,4] were aligned on this point. Expertise-by-experience, although increasingly demanded by research funders, offers no guarantees of improved translation. Co-production, however, in requiring the adoption by researchers and patients of shared aims, would at least ensure a shared vision of what success looks like.

Co-production is now a feature, too, of philosophy of psychiatry. At least in its post-1990s renaissance, both analytic[5] and continental[6] philosophy of psychiatry have adopted co-productive methodologies. In Oxford, a pre-pandemic institutional collaboration between the Faculty of Philosophy and the Mental Health Foundation (a London-based mental health non-governmental organization) remains highly productive. A recently launched joint venture is a Welcome Trust-funded programme on philosophy and new models of public mental health, co-led by a philosopher, A. Bergqvist, and an expert-by-experience, D. Crepaz-Keay.

The wider significance of co-production in philosophy of psychiatry is connected with how the function of philosophy is understood. Stein et al note how the variety of philosophies play out in diverse formulations of complex concepts such as pluralism. This and other similarly diverse formulations point to the function of philosophy being, not to solve complex problems, but rather to *forestall premature closure* on answers, that, although indeed persuasive in the simplifications they encourage, are nonetheless wrong.

The "forestalling premature closure" function of philosophy is important in psychiatry, not least as a barrier to Hoff's above-mentioned "collapses into single message mythologies". Again, co-production offers no guarantees of success. But the indications are positive: co-production itself is after all among the integrative models that Stein et al celebrate; other similarly open systems (such as multidisciplinary teamwork and Darwinian evolution) offer proof-of-principle; and contemporary examples[5,6] document the effectiveness of co-production in philosophy of psychiatry over earlier expert-by-training paradigms. To the extent, therefore, that co-production with experts-by-experience strengthens the role of philosophy in forestalling premature closure on complex problems, philosophy of psychiatry has a role to play in all areas of clinical work and research across mental health as a whole.

Stein et al rightly acknowledge that any review has to balance depth against breadth, an especially difficult task where, as in the humanities, there are no widely-accepted external criteria of excellence, like, say, the evidence hierarchy of evidence-based medicine. This is, perhaps, a "good thing". After all, even the evidence hierarchy is not without its limitations. But, given Stein et al's mention of the North American philosopher H. Putnam, I would suggest a greater attention to his "distinction-without-dichotomy" position on fact and value (since it is by this, not by naturalism, "soft" or otherwise, that values-based practice is underpinned theoretically[7]). To the helpful discussion of the normativity of science, I would add mention of J. Sadler's seminal linguistic analysis of the values guiding DSM[8]. Moreover, since "embodied/4E" is described as representing mental disorders as "disruptions to sense-making", I would suggest an emphasis on the challenge of "delusion", memorably described by the British philosopher of mind N. Eilan as the challenge of "solving simultaneously for understanding and for utter strangeness"[9].

Stein et al have done an important service to the resurgent field of philosophy of psychiatry in demonstrating the still growing success of its collegial approach. Success though comes with challenges – competition for research funding, for prestige, and so forth – and with these in turn come renewed risks of Hoff's "collapses into single message mythologies". In forestalling premature closure on complex problems, philosophy provides the conceptual glue needed to bind together the multiple messages required for an integrated model of mental health of the kind for which Stein et al argue. Highlighting and making fully explicit the importance of co-production between experts-by-experience and experts-by-training, in all areas of mental health research and practice, will ensure that the glue locks tight.

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The author is grateful to D. Crepaz-Keay for his input to this commentary as an expert-by-experience.

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DOI:10.1002/wps.21199

Phenomenology, delusions and justice

The paper by Stein et al[1] offers a clear and magisterial introduction to philosophy of psychiatry, its key advances and its clinical implications. As the authors note, philosophy is often seen as not necessarily having made progress, but the paper shows that this is not the case for philosophy of psychiatry.

Philosophy of psychiatry is both a philosophy of science (similarly to philosophy of physics or biology) and a philosophy of practice and ethics. Indeed, many authors have used philosophy to make sense of, or to interrogate, the changes in our discipline: the hope of the neo-Kraepelinians, the advent of functional neuroimaging, the democratization of psychiatric knowledge, and the partnership with those with lived experience of mental ill health.

The areas that Stein et al cover in their paper are broadly those linked to the philosophy of science and of psychology/mind, and the tradition of "Anglo-American" philosophy. This tradition – inaugurated by Russell, Frege and Moore – has a focus on the analysis of concepts and the study of logic and language. My own philosophical work has been partly in this tradition, but also in the other dominant Western tradition of philosophy, namely "continental" or "European" philosophy.

This tradition grew out of German idealism, neo-Kantianism and phenomenology, and was initially very similar in interests to early analytic philosophy in its study of language, logic and arithmetic. However, through the work of Heidegger, Jaspers and others, it subsequently took the initial phenomenological insights of Husserl, and began using them to understand concrete, historical, lived experience and existential themes.

Such themes reached their apogee in the period after the Second World War, with the existentialism of Sartre and De Beauvoir, and the related work of Merleau-Ponty and Fanon. This work impacted on psychiatry in a series of very direct connections: Heidegger's own teaching of psychiatrists with M. Boss, Binswanger's development of Dasein-analysis, and the influence of phenomenological existentialism on the work of Laing.

However, in parallel to the dominance of phenomenology on European philosophy in the key decades of the 20th century, there are two other key strands to this tradition: the interaction of philosophy with psychoanalysis and with Marxism. Hence, continental philosophy brings with it an interest in "hidden" forces, whether the unconscious or capitalism, that shape human experience, and a more contextualized and historicized idea of the person.

This approach has allowed a more "political" way of thinking about the self and – with post-structuralism, colonial studies, and feminist philosophy – has granted us tools to reflect about issues of intersectionality, oppression, marginalization, and the experience of migration and colonialization, which are relevant to our work as practitioners and researchers[2].

In our recent Renewing Phenomenological Psychopathology project, we have tried to bring some of the insights from the continental philosophy of the later 20th century back into the phenomenological psychopathology of Jaspers and his successors[3]. Much of the "classical" phenomenological psychopathology has been written from a third-person perspective, typically by a European male, trying to describe the structures of the experience of mental illness. With our project we are hoping to increase the international scholarship in the area, to develop new areas of intersection between phenomenology and other academic disciplines and, most importantly, to support those with lived experience who want to work in the area of phenomenology to gain skills through co-production partnerships.

In parallel to this long-standing interest in the phenomenological tradition, I have been fortunate to have worked also in a more "analytic" mode, with a particular interest in the nature of delusions[4]. The definition of delusion has been an area of vigorous debate for philosophy of psychiatry. Influenced by Wittgenstein, Davidson, Dennett, McDowell and others, analytic philosophy provides useful tools to think about rationality. Hence, it comes into conversation with Jaspers' idea of the "un-understandable" nature of primary "true" delusions, and the clinical and empirical interest in how psychosis develops and in continuum models.

The exploration of the distinction between rationality and irrationality, between delusion and unusual beliefs, links with a wider issue in the philosophy of psychiatry, and one that echoes back to Minkowski's critique of Jaspers – namely, that the symptoms and signs of psychopathology are not discrete and "atomistic", but rather form a meaningful coherent whole that informs all of our experience.

An area of potential fertile future research would be to try and chart how much of the way we structure and categorize psychopathology is dependent upon prior historical ideas of faculty psychology, which may now no longer be viable. As an example of this approach, together with Humpston and Broeker[5-7], we have challenged the traditional distinction between passivity experiences, such as thought insertion, and auditory verbal hallucinations, and showed that computational psychiatry may provide a means to empirically demonstrate how symptoms cohere experientially.

The final theme I would like to cover in my reflection on Stein et al's paper returns to ideas of politics and ethics and of lived experience, namely epistemic injustice. Epistemic injustice is a term coined by the philosopher M. Fricker, which grew out of feminist theory. It refers to the lack of justice experienced by a person when his/her ability as a knower is discounted due to non-epistemic factors (for example, gender, ethnicity, age). This is often referred to as "testimonial injustice", and in the literature is accompanied by the idea of "hermeneutic injustice", whereby people unjustly lack the concepts to describe their experience and share that knowledge.

Epistemic injustice provides a rich set of conceptual tools to help us as philosophers of psychiatry and practitioners to understand why the voices of those subject to intersectional marginalization are silenced[8], and importantly, ways to ameliorate that, scaffolding people's ability to be active and valued knowers in their interactions and to maximize their agency in clinical consultations[9]. This area of philosophy is one that we have brought into close proximity with studying real therapeutic encounters, and the experience of young people with mental health problems, and with work covering a range of areas of health care, with important implications for training and education of clinicians.

My own view is that philosophy is an essential ally to the study and practice of psychiatry. As we approach the end of the first quarter of the 21st century, we can see that the hopes of a simple biological, "neo-Kraepelinian", psychiatry are unlikely to be realized, and the suffering and distress caused by mental illness remains. Philosophy brings conceptual clarity, a rigorous questioning, and an expansion of theoretical imagination that can help in addressing the complex set of problems which mental ill health brings, which we as a field have progressed with, and which Stein et al detail and, in their paper, further advance our answers to.

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DOI:10.1002/wps.21202

Philosophy of psychiatry as study of paradigm changes

Philosophy of psychiatry addresses many conceptual topics in psychiatry that lie on the borderline between philosophy, science, culture and clinical practice. Stein et al have produced an excellent critical review of many of these topics and major approaches towards them[1]. In addition, philosophy always has itself as a topic of enquiry – it is eminently self-reflective. Here I will make some observations on what philosophy of psychiatry is.

Briefly put, philosophy studies conceptual issues, but what are they? While there is a long tradition of supposing that concepts are timeless and unchanging, which shows up in some positions in philosophy of psychiatry, the general trend in 20th century philosophy has been to regard concepts as embedded in symbolic systems and practices that vary from time to time and place to place.

An example, to which Stein et al refer several times, is Kuhn's philosophy of science. Science has occasional revolutions in fundamental theory, so-called paradigm shifts, when old assumptions are inadequate for new major problems or discoveries, and are replaced by new kinds of science. These are followed by periods of "normal science", in which the meaning and implications of new theory, methodology and data are worked through[2].

Of special interest to psychiatry and health care generally are paradigm changes in their basic sciences of biology and psychology. Generally recognized revolutions in these sciences occurred in the second half of the 20th century: the genetics/information revolution in biology[3], and the associated cognitive/information revolution in psychology[4]. Since then, normal science within the new paradigms has advanced at pace, with ongoing explorations and developments such as epigenetics and embodied cognition, as discussed by Stein et al.

New paradigms typically usher in new ontology, merging into the traditional subject-matter of philosophy as metaphysics. The above-mentioned paradigm shifts in sciences basic to psychiatry do exactly this. In biology, the 19th century dominant view that physiological processes were (no more than) physics and chemistry was replaced by a new kind of ontology involving coding, information, signalling and regulatory mechanisms[3]. In psychology, the long-standing influence of dualism, underpinning the view that mental processes could not affect the body or behavior, gave way to a new conceptualization of cognitive processes as involved in the regulation of behavior[4].

The appearance of cognitive neuroscience was guaranteed both ways. First, as a biological system like any other, the central nervous system has the dual aspect of physics and chemistry combined with the new science of information processing. Second, it has the particular cognitive function of regulating behavior in the environment. The concept of information has been fundamental in this paradigm shift, with increasing recognition that information is not a representation of already made states of affairs, but is selected, processed and used in ways highly dependent on the needs and goals of the living being.

The ontological status of information as cognition is among the issues currently being worked out under the heading of "embodied cognition", as discussed by Stein et al, illustrating the point made earlier – that scientific revolutions are followed by periods of normal science in which interpretations and consequences of new theory and discoveries within the new paradigm are worked out.

The interconnected paradigm shifts in biology and psychology over the last few decades have major implications for health care sciences. An example is the deconstruction of several interconnected *a priori* supports of reductionism. In addition to energy exchanges and transformations covered by fixed physical-chemical laws, the new paradigms posit system-specific, fragile signalling mechanisms that play fundamental causal roles in regulating the physics and chemistry and other aspects of organismic function and behavior.

This new ontology and theory of causation as regulation removes the basis of presumed reductions of psychology to biology, and biology to physics and chemistry. Physics and chemistry do not break down. So, the old theory – envisaging those alone as basic sciences – never was of any use for conceptualizing (let alone explaining) breakdown, or generally the difference between health and disease, or life and death. Regulatory mechanisms, by contrast, can break down, often do, and eventually always do.

Another, interrelated major aspect of the new paradigms is the dependence of biological and psychological functioning on the environment. For social beings, the social environment, including social status, is highly influential in regulating access to resources necessary for biological and psychological functioning[5]. Stein et al remark several times on the importance of the range of biological, psychological and social factors involved in health and disease, while noting that the biopsychosocial model has been criticized for not being able to deliver specific content, conceptualize cross-domain causal interactions, and resolve causal selection questions[6,7].

Statements of philosophical positions, and comparisons and contrasts between them, typically and perhaps inevitably are simplified by use of names and brief claims. Philosophy of psychiatry, like other philosophical specialties, is replete with such abbreviations: names of general models, such as "biopsychosocial" and the contrasted "biomedical"; brief statements or expressions such as "mental disorders are biological kinds", or "mental disorders are brain disorders"; and abbreviations using terms of philosophical art, often *-isms*, such as "pluralism", "naturalism" and "normativism". While these names and abbreviations have some use, and are probably inevitable in philosophical debates, they do not clarify fundamental questions of ontology, causation and method of the sort becoming explicit in paradigm shifts, as old assumptions no longer work and new ones are needed.

Some paradigm changes in health care involve broader culture rather than science more narrowly conceived. An example is the shift over the past few decades from medical doctors having the sole authority over diagnosis of disorder to the broader community claiming recognition of the right to interpret themselves and their values. A key moment was the successful lobbying by the gay community in the 1970s to have homosexuality removed from the DSM[8]. Plausibly this change owed more to the general emancipatory social movements of the time than to scientific discovery. However, broader culture and science interact, or follow complementary tracks at any one time. The claiming of agency by the gay community in the 1970s coincided in time with the theorizing of personal agency in psychological science.

As the cognitive revolution in psychology spread through its specialty areas, person-level constructs such as appraisals and perceived agency appeared in new causal explanatory models of behavior and well-being[9]. As the implications of new theoretical constructions unfold, concepts of personal agency and cognates such as autonomy are increasingly recognized as important by philosophy of psychiatry, as Stein et al note, with implications in the clinic and in public health[5,6].

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DOI:10.1002/wps.21201

Hallucinating mice, psychotherapy in the brain, and computational psychiatry: the future of psychiatry is now

Stein et al[1] provide a philosophically grounded overview of the conceptual foundations of psychiatry, from its basis in psychopathology to its applications in clinical practice. They emphasize: a) the importance of facts and values in health care; b) the necessity of taking a pluralist approach to science, regarding ontology, explanation and values; and c) the usefulness of "embodied cognition" as an integrative concept in theory and in clinical practice. I have worked as a clinical psychiatrist for over 40 years, with a research focus on systems neuroscience for over the last 30 years, and applaud their thoughts on the foundations of the field. In what follows, I just want to add a few considerations from my personal and scientific perspective.

I endorse Stein et al's points a) and c) wholeheartedly. Whoever maintains that medicine is science, and science is (by definition) only about facts, must be reminded that the terms "pain", "suffering", "illness" and "disease" imply negative valuation, i.e., cannot be understood by anybody who does not grasp what statements like "I do not like x", or "I am so happy because of y" mean. Together with the spatial and temporal finiteness of our minds as *embodied* minds, joy and pain give us agency and purpose, and let us – as the most social primates that evolution brought about – strive for the betterment of our lives. In case of success, psychiatrists are rarely needed; failure, in contrast, calls upon us.

As regards the point b), I want to propose a few considerations. Instead of a pluralist approach, I would like to speak of a multimodal approach with respect to science (ontology and explanation), and of an open and tolerant approach when it comes to cultural differences. Let me explain. There is no British, Chinese, French, San or Papuan science; there is only science. At its empirical connections with reality, science has always been changing, and battles between different schools of thought have been a big part of its history. However, science is remarkably stable at its inner theoretical core. Set theory; Newtonian, Einsteinian and quantum physics; the periodic system, evolution, genetics, etc. have incrementally grown and produced a huge body of knowledge. It is hard to imagine which "ugly fact" would have the epistemic force/weight to contradict any of the approaches just mentioned. Sure, there have always been (and there will always be) statements which are questioned by scientific progress. But, the closer we get from science's empirical connections with reality to its inner core, the smaller the probability of doubt.

In what follows, I want to exemplify a multimodal approach to psychopathology and psychiatry by briefly touching upon three recent domains of research: a) mouse models of various forms of psychopathology that allow to establish causality between brain states and states of mind; b) the concepts of neuromodulation (by small molecules, such as dopamine, acetylcholine, norepinephrine, serotonin and many others) and neuroplasticity (from the synaptic to the cortical level); and c) computational psychiatry as part of artificial intelligence research.

For the larger part of my career, I could not have cared less about mouse models in medicine, especially in psychiatry. They worked for testing new drugs (even though most of our arsenal was discovered by serendipity) and provided some quite limited insights into their mechanisms of action. However, for understanding the core symptoms of psychosis (hallucinations, delusions and formal thought disorder), as well as for providing insights into the interactions between genes and complex human environment, mouse models appeared useless. This has changed completely within the past five years. I will provide some examples.

Eye movement desensitization and reprocessing (EMDR) is a form of psychotherapy used to treat post-traumatic stress disorder (PTSD) with alternating bilateral sensory stimulation (ABS). In order to study its mechanism of action, a mouse model was implemented that allowed the induction of conditioned fear, its extinction, and monitoring the influence of ABS on extinction. In conjunction with ABS, extinction was more pronounced and lasted longer. Once this was established, a neural pathway (from the superior colliculus via the mediodorsal thalamus) which suppressed the activity of fear-encoding cells in the basolateral amygdala, mediating persistent attenuation of fear, could be worked out. "Together, these results reveal the neural circuit that underlies an effective strategy for sustainably attenuating traumatic memories"[2].

In order to study auditory hallucinations in a mouse model[3], mice had to be trained to hallucinate, i.e., firstly, to perceive a salient stimulus (a tone) within random noise (false perception) and, secondly, take this perception more or less for real (reality check). Both responses could be reliably induced. By optogenetic and chemogenetic methods, a neural pathway was discovered, with elevated dopamine levels in the ventral tegmental area and the striatum, where distinct subregions encode different kinds of expectations. "These findings support the idea that hallucinations arise… due to elevated dopamine producing a bias in favor of prior expectations against current sensory evidence"[3].

The term "dissociation" denotes a broad spectrum of states involving perception, thought, consciousness, and the experience of time, space, reality and self. In a mouse model of the effects of drugs that reliably produce a dissociative state, a very specific rhythmic oscillation in layer 5 of the retrosplenial cortex was discovered to be necessary and sufficient for this state. Moreover, in a patient with epilepsy, a similar oscillation was found at a corresponding brain area during the dissociative aura[4]. This finding catapults an ill-defined, little understood and frequently used concept from the 19th into the 21st century.

Within a developmental window in mouse brain development (days 2-9), adversity (murine analogs to human poverty, immigration, neglect and abuse) establishes a circuit which leads to behavioral dysfunction in adulthood (decreased reward sensitivity), very much akin to human PTSD[5].

It is important to realize that optogenetic models allow, for the first time, to establish causality – and not mere correlation – in the realm of mind and brain. Therefore, this method should be highly fruitful in the near future of psychopathology.

The concepts of neuromodulation and neuroplasticity allow neuroscience-based parsimonious explanations of a wide range of mental phenomena, such as acute states of mind (induced by increased, decreased or dysregulated neuromodulatory agents) as well as long-term ("chronic") changes of mind caused by synaptic plasticity. In the mouse model, neuromodulatory changes (increased dopamine in the ventral tegmental area) drive auditory hallucinations, which can be readily treated with dopamine antagonists (in mice and acutely ill patients). Once these experiences become entrenched by synaptic plasticity, they are less dependent upon dopamine hyperactivity and therefore less treatable by antipsychotic agents[6,7].

Finally, neural networks started to be used in computational models of mental phenomena in the late 1980s and 1990s by a few psychiatrists[6-8]. While we expected that computational psychiatry would take off eventually, none of us would have imagined that this new form of artificial intelligence would be applied to anything from deciphering cuneiform script to protein folding, drug design, weather forecasting, as well as designing next-generation hardware and software[9]. Artificial intelligence is not only going to change psychiatry, but to change the world, just as the invention of writing, the printing press, or the Internet.

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DOI:10.1002/wps.21198

Impact of air pollution and climate change on mental health outcomes: an umbrella review of global evidence

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The impact of air pollution and climate change on mental health has recently raised strong concerns. However, a comprehensive overview analyzing the existing evidence while addressing relevant biases is lacking. This umbrella review systematically searched the PubMed/Medline, Scopus and PsycINFO databases (up to June 26, 2023) for any systematic review with meta-analysis investigating the association of air pollution or climate change with mental health outcomes. We used the R metaumbrella package to calculate and stratify the credibility of the evidence according to criteria (i.e., convincing, highly suggestive, suggestive, or weak) that address several biases, complemented by sensitivity analyses. We included 32 systematic reviews with meta-analysis that examined 284 individual studies and 237 associations of exposures to air pollution or climate change hazards and mental health outcomes. Most associations (n=195, 82.3%) involved air pollution, while the rest (n=42, 17.7%) regarded climate change hazards (mostly focusing on temperature: n=35, 14.8%). Mental health outcomes in most associations (n=185, 78.1%) involved mental disorders, followed by suicidal behavior (n=29, 12.4%), access to mental health care services (n=9, 3.7%), mental disorders-related symptomatology (n=8, 3.3%), and multiple categories together (n=6, 2.5%). Twelve associations (5.0%) achieved convincing (class I) or highly suggestive (class II) evidence. Regarding exposures to air pollution, there was convincing (class I) evidence for the association between long-term exposure to solvents and a higher incidence of dementia or cognitive impairment (odds ratio, OR=1.139), and highly suggestive (class II) evidence for the association between long-term exposure to some pollutants and higher risk for cognitive disorders (higher incidence of dementia with high vs. low levels of carbon monoxide, CO: OR=1.587; higher incidence of vascular dementia per 1 μg/m^3 increase of nitrogen oxides, NO$_x$: hazard ratio, HR=1.004). There was also highly suggestive (class II) evidence for the association between exposure to airborne particulate matter with diameter ≤10 μm (PM$_{10}$) during the second trimester of pregnancy and the incidence of post-partum depression (OR=1.023 per 1 μg/m^3 increase); and for the association between short-term exposure to sulfur dioxide (SO$_2$) and schizophrenia relapse (risk ratio, RR=1.005 and 1.004 per 1 μg/m^3 increase, respectively 5 and 7 days after exposure). Regarding climate change hazards, there was highly suggestive (class II) evidence for the association between short-term exposure to increased temperature and suicide- or mental disorders-related mortality (RR=1.024), suicidal behavior (RR=1.012), and hospital access (i.e., hospitalization or emergency department visits) due to suicidal behavior or mental disorders (RR=1.011) or mental disorders only (RR=1.009) (RR values per 1°C increase). There was also highly suggestive (class II) evidence for the association between short-term exposure to increased apparent temperature (i.e., the temperature equivalent perceived by humans) and suicidal behavior (RR=1.01 per 1°C increase). Finally, there was highly suggestive (class II) evidence for the association between the temporal proximity of cyclone exposure and severity of symptoms of post-traumatic stress disorder (r=0.275). Although most of the above associations were small in magnitude, they extend to the entire world population, and are therefore likely to have a substantial impact. This umbrella review classifies and quantifies for the first time the global negative impacts that air pollution and climate change can exert on mental health, identifying evidence-based targets that can inform future research and population health actions.

Key words: Air pollution, climate change, mental health, temperature, dementia, cognitive disorders, post-partum depression, suicide, schizophrenia, post-traumatic stress disorder

(World Psychiatry 2024;23:244–256)

Air pollution, increasing temperatures, and extreme changes in weather patterns represent intertwined elements of a severe global crisis destined to worsen without a fast and radical action[1,2]. They pose a significant physical health threat, leading to an increased risk and/or exacerbation of a variety of diseases, including infectious, allergic, metabolic, neoplastic, respiratory and cardiovascular ones[3].

They also impact mental health, although this relationship has received attention only in more recent years[4]. For example, exposure to air pollution has been associated with a higher risk for cognitive disorders[5], and temperature rise has been found to be related to an increased suicide risk[6]. Extreme weather events such as cyclones, floods or wildfires can foster traumatic experiences, leading to post-traumatic stress disorder (PTSD) in exposed populations[7].

While these environmental exposures can directly affect individuals' mental health, they also appear to exert indirect influences. For example, climate change can affect economic stability, food security, community well-being and physical health, or accelerate migration and conflict, which are themselves key drivers of mental health[8,9].

The direct and indirect impacts of environmental changes on mental health are so concerning, particularly for young generations, that new words have been coined: *solastalgia* (i.e., the distress caused by the transformation and degradation of one's home environment)[10], *ecological grief* (i.e., grief concerning ecological loss)[11], and *eco-anxiety* (i.e., anxiety related to a changing and uncertain environment)[12].

At a scientific level, the associations between these environmental exposures and mental health outcomes have been extensively addressed, leading to an exponential number of publications and, eventually, several systematic reviews[e.g.,5,6,13]. However, findings often conflict across primary studies. For example, one study[14] found a significant association between long-term exposure to airborne particulate matter (PM) and the diagnosis of depression, while another study[15] did not detect this association using a much larger sample. Similarly, while short-term exposure to an increasing temperature has been reported to elevate mortality related to suicide[16], this association was not replicated in another study[17]. Similar inconsistencies are even present between different systematic reviews with meta-analysis. For example, while a systematic review with meta-analysis did not identify an overall association between exposure to PM ≤2.5 μm in diameter ($PM_{2.5}$) and depression[18], another one confirmed it[13].

These contrasting findings may be partially due to different sample sizes[19], small-study effects, reporting biases, large heterogeneity, and inconsistent definition and measuring of relevant exposures. In this context, the existence, direction and magnitude of associations between these environmental exposures and mental health outcomes remain uncertain. The resulting unclear level of evidence and reliable targets hinder further research and prevent population health actions aimed to mitigate the impact of these exposures on mental health.

The present work aims to fill these gaps by providing a comprehensive umbrella review to systematically examine and classify the evidence associating air pollution and climate change with mental health outcomes globally. To this end, a standardization of units of measurement was performed, and the R *metaumbrella* package was used to calculate and stratify the credibility of the evidence according to criteria that address several biases.

The evidence-based classification provided by this umbrella review is designed to support sound recommendations for the next generation of research and population-level approaches addressing the impact of air pollution and climate change on mental health.

METHODS

We conducted the present umbrella review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[20], and pre-registered its protocol at https://osf.io/rgjdp/?view_only=d60ab9238c714014ae148acde5e55ad2.

Search strategy

We systematically searched the PubMed/Medline, Scopus and PsycINFO databases from inception to June 26, 2023. The search strategy included terms related to air pollution and climate change and to mental health outcomes (see supplementary information). We hand-searched the references of each included review, textbooks, and other materials to identify potential additional systematic reviews with meta-analysis not captured by the original search string.

Exposures and outcomes

Air pollution and climate change were pragmatically operationalized according to the definitions provided in each systematic review with meta-analysis. They were referred to the general population, unless specifically mentioned (e.g., air pollution during pregnancy).

Mental health outcomes included: a) mental disorders grouped into ICD-10 diagnostic blocks: organic mental disorders; mental and behavioral disorders due to psychoactive substance use; schizophrenia, schizotypal and delusional disorders; mood (affective) disorders; neurotic, stress-related and somatoform disorders; behavioral syndromes associated with psychological disturbances and physical factors; disorders of adult personality and behavior; mental retardation; disorders of psychological development; and behavioral and emotional disorders with onset usually occurring in childhood and adolescence; b) mental disorders-related symptomatology (e.g., symptoms or manifestations associated with a mental disorder, such as depressive or anxiety symptoms); c) suicidal behavior; d) access to mental health care services.

Inclusion and exclusion criteria

We considered eligible for inclusion any systematic review with meta-analysis including observational studies (both cross-sectional and longitudinal), that: a) investigated the association of either air pollution or climate change, or both, with any mental health outcome (as defined above); and b) compared exposed vs. non-exposed populations, or populations at different levels of exposure. Each association had to be based on at least two individual studies to be eligible for inclusion.

We excluded: a) any publication other than systematic reviews with meta-analysis, including systematic reviews without meta-analysis, and meta-analyses that did not follow a systematic search procedure; b) systematic reviews with meta-analysis including only interventional studies; c) systematic reviews with meta-analysis including only studies providing prevalence data in a single group; d) systematic reviews with meta-analysis including only pre-post studies; e) systematic reviews with meta-analysis that were not related to our research question; f) grey literature (i.e., publications that did not undergo a peer review process, such as doctoral theses and conference abstracts); g) systematic reviews with meta-analysis that were retracted after publication; h) systematic reviews with meta-analysis reporting the same associations of other systematic reviews with meta-analysis that were more comprehensive or recent; i) systematic reviews with meta-analysis that did not provide sufficient data to conduct the umbrella review.

Selection of systematic reviews with meta-analysis and data extraction

Three authors (MDP, VO, GF) independently assessed systematic reviews with meta-analysis of potential interest at the title, abstract and full-text levels. Any disagreement was resolved by consensus, and another author (JR, PFP) was consulted when an agreement could not be reached. The same three authors independently extracted information from the included reviews.

At a single systematic review with meta-analysis level, we recorded the first author, publication year, number of included individual studies, type of exposure, type of mental health outcome, and type of effect size considered – i.e., odds ratio (OR), hazard ratio (HR), or risk ratio (RR). For time-dependent exposures (i.e., long-term and short-term ones), we recorded the time frame considered for each specific association. Long-term exposures were considered to be those lasting months or years, while short-term exposures were those lasting days or weeks (generally less than 30 days).

At an individual study level, we recorded the first author, publication year, study design, any measure useful to calculate the effect size, and dependencies in the data (multiple outcomes from the same group, or multiple groups in a study).

Quality of evidence

We used A Measurement Tool To Assess Systematic Reviews (AMSTAR-2)[21] to assess the quality of the included systematic reviews with meta-analysis. We classified methodological quality as "high" (no critical weakness and no more than one non-critical weakness); "moderate" (no critical weakness but more than one non-critical weaknesses); "low" (one critical weakness); and "critically low" (more than one critical weaknesses)[21].

Statistical analyses

During the early phase of data collection, we noticed that the included systematic reviews with meta-analysis investigated the associations between air pollution or climate change exposures and mental health outcomes either continuously (e.g., suicide mortality increases per each 5°C increase in temperature) or binarily (e.g., differences in dementia incidence between individuals highly exposed and those not, or little, exposed to solvents). Systematic reviews with meta-analysis investigating continuous associations were heterogeneous with regards to the exposure intervals used to report the results. To overcome this problem, we converted all intervals to one unit in the International System of Units (e.g., change per 1°C increase or change per 1 $\mu g/m^3$ increase). This was performed by dividing the logarithm of the RR or OR by the number of international system units[22]. When a review analyzed continuous and binary data together, we meta-analyzed the individual studies providing continuous data separately from those providing binary data.

We assessed the credibility of the associations according to recognized international criteria[23-26]. Specifically, we classified each association as convincing (class I), highly suggestive (class II), suggestive (class III), or weak (class IV). If an association was not significant, we classified it as such. Class I requires more than 1,000 cases, $p<10^{-6}$, no evidence of small-study effects or excess of significance bias, prediction interval not including the null value, the largest study nominally significant, and not large heterogeneity (i.e., $I^2< 50\%$). Class II requires more than 1,000 cases, $p<10^{-6}$, and the largest study nominally significant. Class III requires more than 1,000 cases and $p<10^{-3}$. Class IV only requires $p<0.05$.

We conducted a sensitivity analysis that included only longitudinal studies, to test the impact of the study design on the findings and ensure that, in the associations, the air pollution and climate change exposures reliably preceded the mental health outcomes.

We performed a complementary analysis by inferring the increase in the rates of selected mental health outcomes (i.e., those that were found to be associated with temperature increase with class I or II evidence) as a function of the earth yearly average land temperature anomaly. We retrieved the earth yearly average land temperature from 1750 to 2022 from Berkeley Earth (https://berkeleyearth.org), and calculated the earth yearly land temperature anomaly by subtracting from the observed 1800-2022 land temperature the mean land temperature in the pre-industrial period (i.e., from 1750 to 1799).

We used the corresponding RR derived from the umbrella review to make these inferences. For instance, if a mental health outcome had RR=1.01 per 1°C increase and the land temperature anomaly in a given year was 1°, we inferred 1% increase that year.

We estimated the yearly land temperature increase rate in the last decades and projected this rate up to 2050 (i.e., assuming that the land temperature anomaly will increase the same amount each year). Up to 2022, we derived the confidence intervals (CIs) of the inferred increase in mental health outcomes directly from the CIs of the present umbrella review. CIs from 2023 to 2050 were estimated via Monte-Carlo simulations of the combination of our CIs with the prediction intervals of land temperature anomaly.

We performed all umbrella calculations with the R package *metaumbrella*[27], which was developed by our group and first applied in a previous publication in this journal[23]. This is the first comprehensive package that allows conducting umbrella reviews by automatically performing all the necessary calculations and subsequently classifying the credibility of the evidence.

RESULTS

Literature search and studies identified

We identified 3,582 references. After duplicate removal, we screened 2,421 at the title and abstract level and 132 at the full-text level. A final set of 32 systematic reviews with meta-analysis [5,6,13,28-56], encompassing 284 individual studies (231 longitudinal and 53 cross-sectional), were included in the umbrella review (see Figure 1 and Table 1). The excluded studies are detailed in the supplementary information.

The individual studies included samples from the US (n=74), China (n=41), the UK (n=21), South Korea (n=20), Canada (n=19), Taiwan (n=13), Germany (n=12), The Netherlands (n=11), Spain (n=11), Sweden (n=11), France (n=8), Australia (n=6), Italy (n=6), Hong Kong (n=4), Japan (n=4), Denmark (n=3), Finland (n=3), Iran (n=3), Israel (n=3), Norway (n=3), Belgium (n=2), Brazil (n=2), India (n=2), Mexico (n=2), New Zealand (n=2), Poland

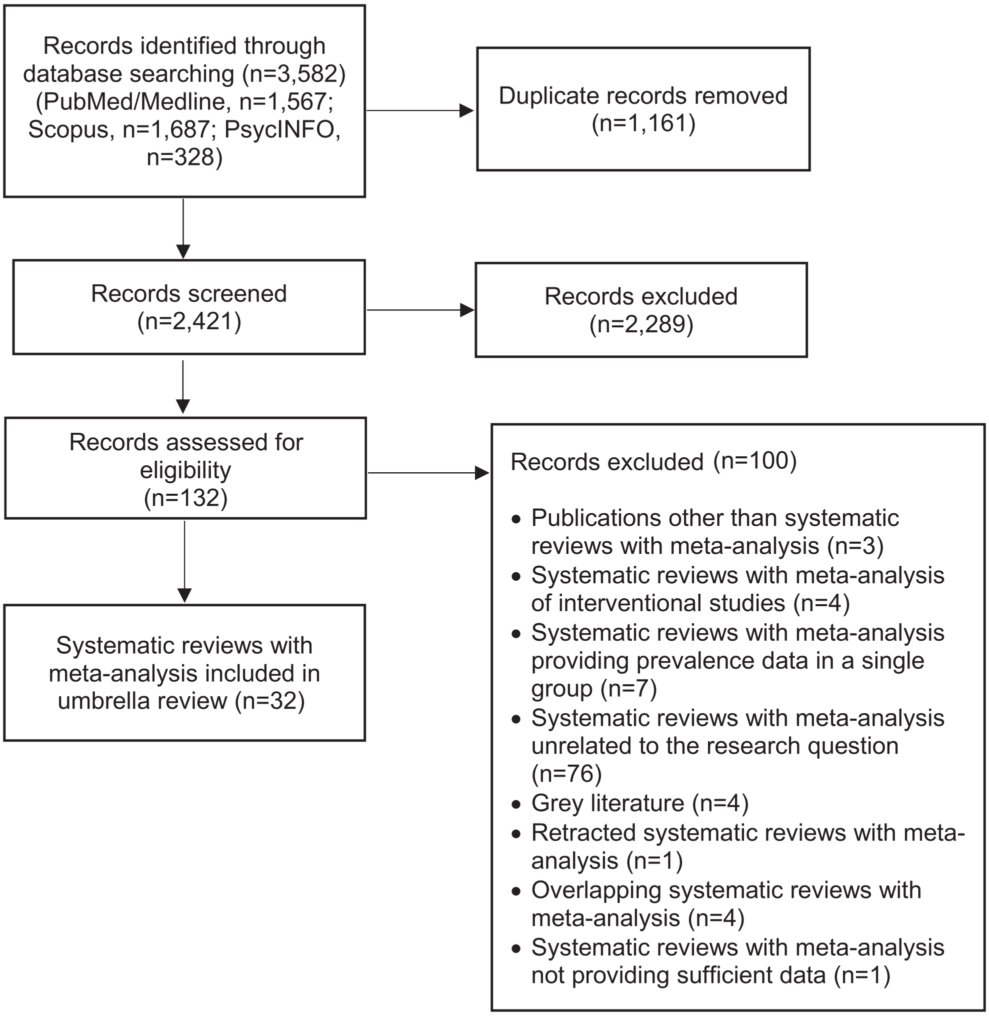

Figure 1 PRISMA flow chart

(n=2), Portugal (n=2), Austria (n=1), Bangladesh (n=1), Colombia (n=1), Ghana (n=1), Greece (n=1), Greenland (n=1), Kazakhstan (n=1), Nigeria (n=1), Slovakia (n=1), South Africa (n=1), Sri Lanka (n=1), Switzerland (n=1), Turkey (n=1) and Vietnam (n=1). These samples do not sum to 284 because an individual study may have included multiple samples from different countries.

Characteristics of included systematic reviews with meta-analysis

Of the systematic reviews with meta-analysis, 25 focused on the mental health impact of air pollution[5,13,31,33-41,44-46,48-56]; six on the impact of climate change hazards[6,29,30,32,43,47]; and one on both[42].

Mental health outcomes included mental disorders[5,13,30,33-35,37-41,44-46,48-50,52,53,55,56]; suicidal behavior[6,31,36,42]; mental disorders-related symptomatology[32]; access to mental health care services[28], both mental disorders and mental disorders-related symptomatology[29,51,54]; and mental disorders, suicidal behavior, and access to mental health care services[47].

Associations of air pollution or climate change exposures and mental health outcomes

We included and analyzed 237 associations of exposures to air pollution or climate change hazards and mental health outcomes. Of these associations, 195 (82.3%) concerned air pollution, and 42 (17.7%) involved climate change hazards.

The associations concerning air pollution focused, in decreasing order of frequency, on $PM_{2.5}$ (n=40, 16.9%), airborne particular matter ≤10 µm in diameter (PM_{10}) (n=35, 14.8%), nitrogen dioxide (NO_2) (n=32, 13.6%), ozone (O_3) (n=22, 9.3%), sulfur dioxide (SO_2) (n=17, 7.2%), carbon monoxide (CO) (n=11, 4.6%), PM coarse (n=8, 3.4%), nitrogen oxides (NO_x) (n=6, 2.5%), solvents (n=5, 2.1%), pesticides (n=3, 1.3%), metals (n=2, 0.8%), solid fuels (n=1, 0.4%), diesel PM (n=1, 0.4%), polycyclic aromatic hydrocarbons (n=1, 0.4%), or multiple pollutants together (n=11, 4.6%).

The associations concerning climate change hazards focused

Table 1 Characteristics of the systematic reviews with meta-analysis included in the umbrella review

	Studies included	Sample size	Associations included	Exposure	Mental health outcome
Abolhasani et al[28]	4	86,516,610	1	Air pollution	Hospitalization due to dementia
Borroni et al[13]	39	4,659,344	12	Air pollution	Depression
Braithwaite et al[31]	4	34,451	1	Air pollution	Suicidal behavior (mortality)
Cheng et al[33]	19	40,217,872	2	Air pollution	Dementia, vascular dementia
Chun et al[34]	4	91,363	1	Air pollution	Autism spectrum disorder
Bernardina Dalla et al[35]	11	95,607	5	Air pollution	ADHD
Davoudi et al[36]	9	1,532,847	13	Air pollution	Suicidal behavior (mortality)
Dhiman et al[37]	4	578,383	1	Air pollution	Alzheimer's disease
Dutheil et al[38]	26	748,247	14	Air pollution	Autism spectrum disorder
Flores-Pajot et al[39]	4	141,061	9	Air pollution	Autism spectrum disorder
Fu et al[40]	15	218,487	2	Air pollution	Autism spectrum disorder, mild cognitive impairment
Fu et al[5]	8	13,528,702	2	Air pollution	Alzheimer's disease
Gong et al[41]	14	77,053,755	4	Air pollution	Alzheimer's disease, dementia, vascular dementia
Li et al[44]	9	70,214	1	Air pollution	Depression
Lin et al[45]	17	645,663	10	Air pollution	ADHD, autism spectrum disorder
Liu et al[46]	27	1,009,799	4	Air pollution	Autism spectrum disorder
Pourhoseini et al[48]	3	31,587	20	Air pollution	Post-partum depression
Song et al[49]	13	27,055	40	Air pollution	Schizophrenia
Tang et al[50]	12	13,158,086	3	Air pollution	Alzheimer's disease, dementia, vascular dementia
Trushna et al[51]	9	445,562	4	Air pollution	Anxiety disorders, psychological stress
Wilker et al[52]	12	16,357,675	2	Air pollution	Dementia
Yu et al[53]	10	2,703,941	2	Air pollution	Cognitive impairment, dementia
Zeng et al[54]	12	289,066	11	Air pollution	Depression, depressive symptoms
Zhang et al[55]	5	102,925	3	Air pollution	ADHD
Zhao et al[56]	52	80,986,923	23	Air pollution	Alzheimer's disease, cognitive impairment, dementia, vascular dementia
Beaglehole et al[29]	2	1,144	2	Landslides, wildfires	Mental disorders, psychological distress
Bonde et al[30]	4	2,702	1	Cyclones, floods, tsunami	Depression
Chan et al[32]	8	2,934	1	Cyclones	PTSD symptoms
Frangione et al[6]	20	3,021,622	7	Precipitation, temperature	Suicidal behavior (mortality or attempts)
Li et al[43]	32	8,179,080	15	Barometric pressure, sunshine duration, temperature	Mental disorders; mood disorders; neurotic, stress-related and somatoform disorders; schizophrenia
Liu et al[47]	30	3,159,423	14	Temperature	Mental disorders, organic mental disorders, schizophrenia, substance-related mental disorders, suicidal behavior (mortality), hospital access
Heo et al[42]	29	2,635,678	7	Air pollution, temperature	Suicidal behavior (mortality, attempts or ideation, or self-harm)

ADHD – attention-deficit/hyperactivity disorder, PTSD – post-traumatic stress disorder

on temperature (n=35, 14.8%), barometric pressure (n=1, 0.4%), cyclones (n=1, 0.4%), precipitation (n=1, 0.4%), sunshine duration (n=1, 0.4%), or multiple hazards together (n=3, 1.3%).

Regarding mental health outcomes, associations focused, in decreasing order of frequency, on mental disorders (n=185, 78.1%), suicidal behavior (n=29, 12.4%), access to mental health care services (n=9, 3.7%), mental disorders-related symptomatology (n=8, 3.3%), or multiple categories together (n=6, 2.5%).

Associations involving mental disorders encompassed organic mental disorders (n=42, 17.7%); schizophrenia (n=42, 17.7%); autism spectrum disorder (n=38, 16%); mood disorders (n=36, 15.3%); attention-deficit/hyperactivity disorder (n=9, 3.8%); neurotic, stress-related and somatoform disorders (n=5, 2.1%); substance-related mental disorders (n=1, 0.4%); and multiple mental disorders together (n=12, 5.1%).

Suicidal behavior encompassed suicide mortality (n=15, 6.4%); suicide mortality, attempts or ideation, or self-harm (n=7, 3.0%); and suicide mortality or attempts (n=7, 3.0%). Mental disorders-related symptomatology encompassed depressive symptoms (n=5, 2.1%), psychological distress (n=2, 0.8%), and PTSD symptoms (n=1, 0.4%). Access to mental health care services encompassed hospital access (i.e., hospitalization or emergency department visits) (n=8, 3.3%) and hospitalization only (n=1, 0.4%) for specific mental conditions.

Convincing (class I) and highly suggestive (class II) associations

Among the 237 associations included in the umbrella review, one (0.4%) reached a convincing level of credibility (class I), and eleven (4.6%) reached a highly suggestive level of credibility (class II) (see Table 2).

The only class I association was that between long-term exposure to solvents and a higher incidence of dementia or cognitive impairment (OR=1.139; 95% CI: 1.090-1.191).

Long-term exposure to high vs. low CO levels was associated with an increased incidence of dementia (OR=1.587; 95% CI: 1.389-1.812, class II). Long-term exposure to NO_x increase was associated with a higher incidence of vascular dementia (HR=1.004 per 1 $\mu g/m^3$, 95% CI: 1.003-1.005, class II).

An increase in PM_{10} exposure during the second trimester of pregnancy was associated with an increased risk of developing post-partum depression (OR=1.023 per 1 $\mu g/m^3$ increase; 95% CI: 1.014-1.033, class II). An increase in short-term exposure to SO_2 was associated with a higher risk of relapse of schizophrenia (RR=1.005 per 1 $\mu g/m^3$, 95% CI: 1.004-1.006; and RR=1.004 per 1 $\mu g/m^3$, 95% CI: 1.003-1.005, respectively 5 and 7 days after exposure; class II).

Short-term exposure to temperature increase was associated with a higher risk of suicide- or mental disorders-related mortality (RR=1.024 per 1°C increase; 95% CI: 1.015-1.033, class II). It was also associated with a higher risk of suicidal behavior (RR=1.012 per 1°C increase; 95% CI: 1.011-1.014, class II), a higher risk of hospital access due to suicidal behavior or mental disorders (RR=1.011 per 1°C increase; 95% CI: 1.008-1.015, class II), and a higher risk of

Table 2 Convincing (class I) and highly suggestive (class II) associations

Exposure	Mental health outcome		Estimate (95% CIs)	p	N	I^2	PIs	SSE/ESB	LS	Class
Solvents (high vs. low exposure, long-term)	Incidence of dementia or cognitive impairment		OR=1.139 (1.090-1.191)	$<10^{-6}$	19,379	41%	SIG	No/No	Yes	I
CO (high vs. low levels, long-term)	Incidence of dementia		OR=1.587 (1.389-1.812)	$<10^{-6}$	2,629	0%	NS	No/No	Yes	II
NO_X (1 $\mu g/m^3$ increase, long-term)	Incidence of vascular dementia		HR=1.004 (1.003-1.005)	$<10^{-6}$	7,608	0%	-	-/-	Yes	II
PM_{10} (1 $\mu g/m^3$ increase, during second trimester of pregnancy)	Incidence of post-partum depression		OR=1.023 (1.014-1.033)	$<10^{-6}$	2,211	36%	-	-/-	Yes	II
SO_2 (1 $\mu g/m^3$ increase, short-term)	Relapse of schizophrenia	5 days after exposure	RR=1.005 (1.004-1.006)	$<10^{-6}$	8,682	0%	-	-/-	Yes	II
		7 days after exposure	RR=1.004 (1.003-1.005)	$<10^{-6}$	8,682	0%	-	-/-	Yes	II
Temperature (1°C increase, short-term)	Suicide- or mental disorders-related mortality		RR=1.024 (1.015-1.033)	$<10^{-6}$	1,559,502	75%	NS	Yes/Yes	Yes	II
	Suicidal behavior (mortality, attempts or ideation, or self-harm)		RR=1.012 (1.011-1.014)	$<10^{-6}$	2,260,123	70%	SIG	No/No	Yes	II
	Hospital access due to suicidal behavior or mental disorders		RR=1.011 (1.008-1.015)	$<10^{-6}$	1,052,237	86%	NS	Yes/Yes	Yes	II
	Hospital access due to mental disorders only		RR=1.009 (1.006-1.012)	$<10^{-6}$	640,651	78%	NS	Yes/Yes	Yes	II
Mean apparent temperature (1°C increase, short-term)	Suicidal behavior (mortality or attempts)		RR=1.010 (1.009-1.011)	$<10^{-6}$	323,163	0%	-	-/-	Yes	II
Cyclone exposure (temporal proximity)	PTSD symptoms severity		r=0.275 (0.189-0.357)	$<10^{-6}$	≥1,000	75%	SIG	No/No	Yes	II

CO – carbon monoxide, PM_{10} – airborne particulate matter with diameter ≤10 μm, NO_x – nitrogen oxides, SO_2 – sulfur dioxide, PTSD – post-traumatic stress disorder, OR – odds ratio, HR – hazard ratio, RR – risk ratio, PIs – prediction intervals, SSE – small study effect, ESB – excess significant bias, LS – largest study with significant effect, SIG – significant, NS – not significant hospital access due to mental disorders only (RR=1.009 per 1°C increase; 95% CI: 1.006-1.012, class II).

A short-term exposure to apparent temperature increase ("apparent" is defined as the temperature equivalent perceived by humans[57]) was associated with a higher risk of suicidal behavior (RR=1.010 per 1°C increase; 95% CI: 1.009-1.011, class II).

Higher temporal proximity of cyclone exposure (i.e., fewer months since exposure) was associated with higher severity of PTSD symptoms (r=0.275; 95% CI: 0.189-0.357, class II).

Sensitivity and complementary analyses

The sensitivity analysis that included only longitudinal studies confirmed all the above class I and class II associations, except that between temporal proximity of cyclone exposure and PTSD severity, which was based on cross-sectional studies only.

One additional association reached class II evidence in the longitudinal analysis. This was the association between exposure to solid fuels (e.g., biomass, firewood) and a higher incidence of depression (OR=1.27; 95% CI: 1.16-1.39, previously class III) (see also supplementary information).

Figure 2 shows, according to the above data, how much earth yearly land temperature anomaly (i.e., the increase in land temperature compared to the pre-industrial period) may have increased the relevant mental health outcomes (e.g., suicide- or mental disorders-related mortality) up to 2022, and the potential increase in the upcoming years. Our estimate indicates that this increased mortality is already ~5% now and will reach ~7% (95% CI: 4.2- 9.7) in 2050.

Suggestive (class III), weak (class IV), and not significant associations

Among the 237 associations between exposures to air pollution or climate change hazards and mental health outcomes included in this umbrella review, 24 (10.1%) reached a suggestive level of credibility (class III); 65 (27.3%) reached a weak level of credibility (class IV); and 136 (57.6%) were not significant (see also supplementary information).

Quality of included systematic reviews with meta-analysis

The quality of all the included systematic reviews with meta-analysis was rated as "low" or "critically low". Specifically, AMSTAR-2 item 2 (i.e., presence of protocol) was not satisfied by 14 reviews (43.8%); item 4 (i.e., comprehensive literature search) by 15 reviews (46.9%); item 7 (i.e., list of studies excluded with reasons) by 31 reviews (96.9%); item 9 (i.e., satisfactory assessment of risk of bias) by four reviews (12.5%); item 13 (i.e., taking into account risk of bias in discussion of the results) by 15 reviews (46.9%); and item 15 (i.e., exploring and taking into account publication bias in discussion of results) by 17 reviews (53.1%) (see also supplementary information).

DISCUSSION

The present umbrella review comprehensively summarizes and assesses for the first time the credibility of the existing evidence on the impact of air pollution and climate change on mental health outcomes. Evidence emerged that some of these exposures are associated with mental health outcomes. Higher levels of specific air pollutants were associated with a higher risk of dementia or cognitive impairment (class I), cognitive disorders (class II), postpartum depression (class II), and schizophrenia relapse (class II). Temperature increase was associated with an increase in suicidal behavior, suicide- or mental disorders-related mortality; and hospital access due to suicidal behavior or mental disorders, or mental disorders only (class II).

A first strength of this umbrella review is the extensive database (284 individual studies) encompassing all continents, including the Global South, and therefore providing a global picture. Furthermore, we included the largest ever set of associations (n=237), systematically appraised with evidence-based classification criteria that assess existing biases. To provide more stringent evidence, we converted all the exposure intervals to one unit in the International System of Units; applied a sensitivity analysis restricted to longitudinal studies; and conducted a complementary analysis to predict the future impact of associations involving increased temperature. The state-of-the-art umbrella review method was further enhanced by using the *metaumbrella* package[27], which facilitates large syntheses across multiple databases and association measures.

The strongest finding of this umbrella review is the convincing (class I) association between higher levels of exposure to solvents and a higher risk of developing dementia or cognitive impairment. Solvents (e.g., toluene, acetone, xylene, hexane, heptane, and ethyl acetate) can release volatile organic compounds into the atmosphere, contributing to the formation of ground-level O_3 and smog[58]. They are also directly toxic to many parts of the body, with symptoms ranging from skin irritation, headaches and blurred vision, to loss of consciousness and death[59]. The solvent most studied at the central nervous system level is toluene, whose adverse effects are manifested with acute encephalopathy and white matter damage, multifocal myelin loss, and macrophage accumulation[60,61].

The main uses of solvents include paints, paint strippers, inks, and dry cleaning, and they continue to pose serious health risks, especially in low- and middle-income countries, where alternatives to these materials are difficult to find for construction and manufacturing processes[62,63]. Because of their widespread use, solvent emissions are expected to approximately double by 2030[64], which is alarming considering their environmental risk[58] and potential impact on climate change[65].

We also found highly suggestive (class II) evidence for a higher incidence of cognitive disorders with CO and NO_X increased exposure. CO is among the main gases that trap heat in the atmo-

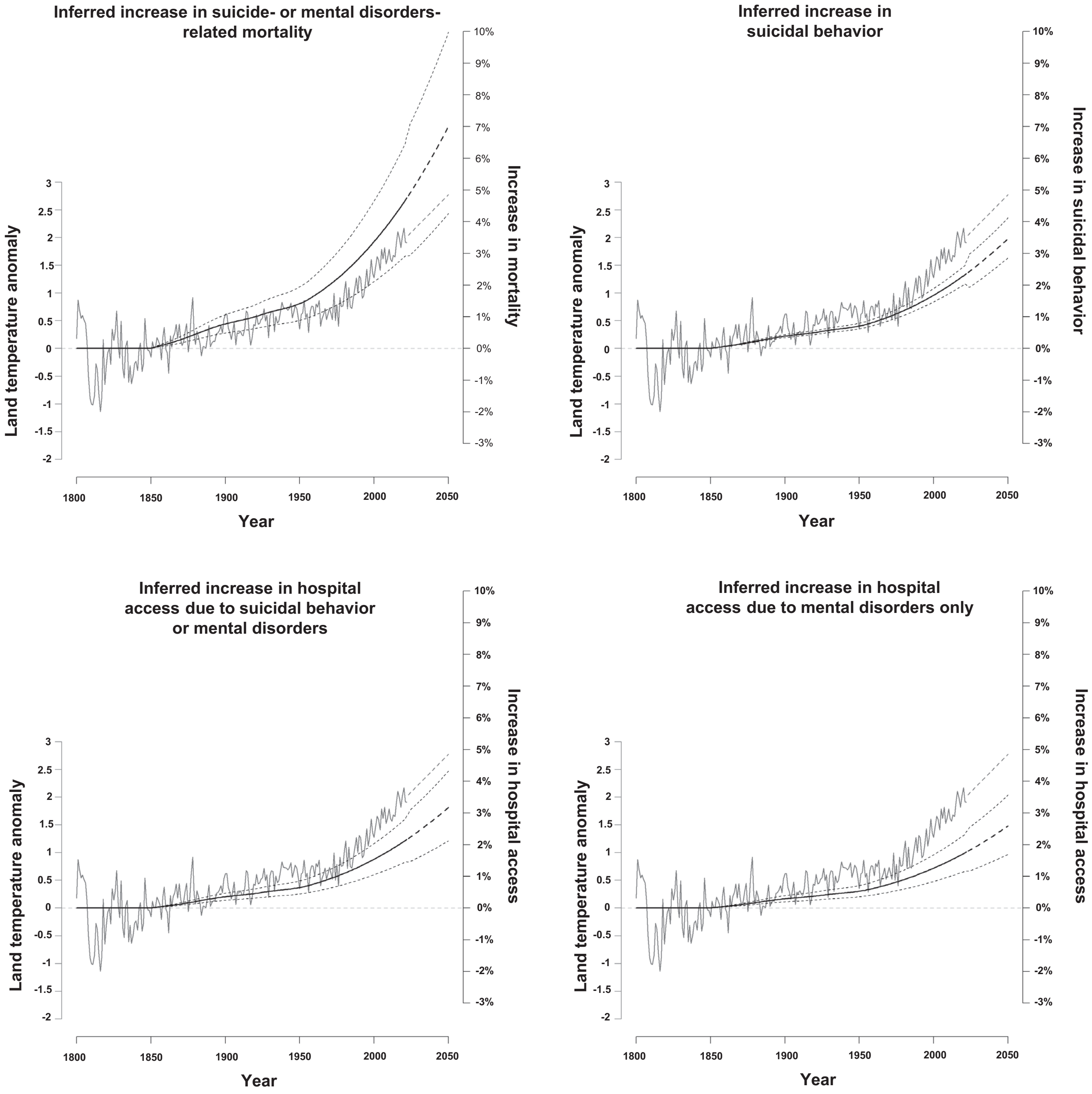

Figure 2 Inferred increase in mental health outcomes associated with temperature anomaly (earth yearly land temperature increase compared to average of pre-industrial period). The fluctuating line represents the temperature anomaly. The steady line represents the relative risks (RRs) corresponding to temperature anomalies according to the RRs from the umbrella review. The dashed lines represent the confidence intervals derived from the umbrella review up to 2022, and estimated via Monte-Carlo simulation for 2023-2050.

sphere (greenhouse gases), making the planet warmer and "thickening the Earth's atmospheric blanket"[66]. It is mainly produced by human activity (e.g., burning fossil fuels, solid waste, chemical reactions)[66]. NO_x are gases mainly produced during the combustion of fossil fuels. They are precursors for the formation of O_3, which has adverse effects on the environment[67].

CO and NOx share toxic brain effects with other air pollutants[68,69], including neuroinflammation, neurodegeneration, and cerebral vascular damage[70]. These air pollutants can enter the organism through the respiratory tract[71]. Once in the body, they may activate the inflammatory system and contribute to activation of microglia[72], oxidative stress, and cell damage or death[73,74]. The current findings are therefore consistent with those reported by population-based cohort studies indicating that living near major roads is associated with a higher incidence of dementia[75].

It is also worth noticing that the association between CO and dementia did not reach class I evidence because of the prediction intervals that crossed the null value. The package *metaumbrella* that we used to perform the analyses estimates the prediction intervals through a t-distribution with k-2 degrees of freedom[76]. This method provides conservative results compared to other accepted methods, such as constructing prediction intervals using a normal distribution, which would have elevated this association to class I evidence.

Furthermore, we found evidence (class II) that the incidence of post-partum depression increased with PM_{10} exposure during the second trimester of pregnancy. PM_{10} can contain harmful substances (e.g., benzopyrenes, furans, dioxins, and carcinogenic heavy metals) that can be inhaled. These particles are essentially produced by human sources (e.g., fuel combustion, heating, vehicles, biomass burning, and industrial activities), and their detrimental effects on physical health (e.g., the respiratory system) are well established[77]. It is possible that their effect on mental health is mediated by an increase in stress hormone levels[78].

Indeed, there is some evidence that exposure to these particles increases cortisol levels[79]. These levels tend to be elevated during the second and third trimesters of pregnancy[80] (when there is an increased secretion of corticotropin-releasing hormone from the placenta) and are associated with the risk of post-partum depression[81]. Thus, the interplay of these pollutants with the physiological increase in stress hormones may account for the increased incidence of post-partum depression. Future empirical research is, however, needed to confirm this hypothesis.

We also found evidence (class II) for a higher risk of relapse in patients with schizophrenia shortly (5 to 7 days) after exposure to increased levels of SO_2. This is a toxic gas naturally released by volcanic activity and in the production of sulfuric acid. It can also be used as a disinfectant, a refrigerant, a reducing agent, a bleach, and a food preservative. It can modulate climate change processes[82] and has also been associated with increased all-cause mortality[83], higher risk of respiratory disease, and increased likelihood of cardiovascular events[84], including stroke[85].

However, the mechanism linking short-term SO_2 exposure to physical health outcomes has yet to be established. While it is possible that this exposure induces increased inflammation, potentially exacerbating or triggering new symptoms in individuals with schizophrenia, this remains speculative, and there is no conclusive evidence linking inflammatory markers to relapse in this disorder[86]. While the nature of this association requires further empirical studies, this finding conceptually supports the profound socio-environmental dimension and origin of schizophrenia, which has been previously appraised by our and other groups[26,87].

Overall, these findings align with the detrimental role of air pollution as a major global environmental and physical health problem, contributing to more than 8 million deaths per year[88]. It is estimated that the world's entire population (99%) breathes air that exceeds the pollution limits recommended by the World Health Organization (WHO)[89]. The current study adds to this evidence by indicating that air pollution has a negative impact also on mental health worldwide.

Innovative policies and initiatives have recently been launched to improve air quality, monitor pollutants, and strengthen cooperation between countries, such as the Forum for International Cooperation on Air Pollution[90], the Task Force on Techno-Economic Issues (TFTEI) Clearing House of Control Technologies[91], and the WHO Air Quality Guidelines[92]. Future upgrades of these policies could consider the associations emerging from this umbrella review as outcome measures to map their global impact on mental health.

The second main finding of this study is the highly suggestive (class II) evidence for an association between temperature increase and several mental health outcomes, such as suicide- or mental disorders-related mortality, suicidal behavior; and hospital access due to suicidal behavior or mental disorders, or mental disorders only. These are core real-world outcomes of high clinical relevance, and their associations with an increasing temperature may represent an alarming finding.

In recent years, global warming has become one of the highest concerns, particularly for young people[93]. According to the Intergovernmental Panel on Climate Change, the global mean surface temperature in 2011-2020 was 1.09°C higher than in 1850-1900[94]. Recent reports revealed that 2023 was the hottest year on record, with global temperatures being close to the Paris Agreement limit of 1.5°C[95]. This finding is even more concerning when considering that temperatures on land rise faster (1.59°C) than those in the ocean (0.88°C), emphasizing the impact on humans[94]. The greenhouse effect caused by specific pollutants is the main driver of temperature increase and global warming[96].

In this scenario, we demonstrate here that global warming negatively affects mental health. However, despite the huge magnitude of the problem, the biological mechanisms underlying this association remain unknown and likely involve complex multifactorial relationships[97-99]. Some evidence suggests that exposure to hot temperatures may directly affect brain function, with alterations in proper oxygenation and permeability of the blood-brain barrier. Other studies implicate alterations in neurotransmitters[97], or suggest that higher temperatures may directly worsen mood, leading people to feel more irritable and stressed, and amplifying symptoms of mental disorders[100].

There are also numerous indirect effects of global warming on mental health outcomes. For example, in 2022, 84% of refugees and asylum seekers fled from highly climate-fueled crises and climate-vulnerable countries (e.g., because of droughts and increases in sea levels), representing "environmental refugees"[101]. Short-term projections up to 2040 estimate that the average global surface temperature will increase by 0.4-1°C, and long-term projections suggest a temperature increase of up to 4.8°C in a high-emissions scenario[102]. Accordingly, the United Nations' projections predict that the environmental refugee situation will significantly deteriorate in the future.

To further support these projections and therefore inform future global initiatives that could tackle these issues, we estimated the future increase in suicide- or mental disorders-related mortality associated with the predicted increase in land temperature. We inferred that this increased mortality is already ~5% now (compared with pre-industrial levels) and will reach ~7% in 2050.

This umbrella review also found evidence (class II) that cyclones are increasing the severity of PTSD. These are large masses of air rotating around an area of low pressure, generally associated with heavy rainfalls, that can cause massive destruction to human populations in their path. In fact, they can cause both physical and psychological damage, interrupting daily routines and forcing dramatic evacuation and sheltering[103]. These events, along with the significant economic loss and adversity experienced in the aftermath, may constitute severe traumatic events associated with the development of PTSD[104]. However, this umbrella review calls for further studies and future confirmation, as the available evidence was not confirmed in sensitivity analyses.

The present work has some limitations. First, as an umbrella review, the evidence presented is limited to that found in systematic reviews with meta-analysis, not considering associations that have not been meta-analyzed. Second, the quality of the included systematic reviews with meta-analysis was generally low, mainly because of inadequate discussion and investigation of sources of heterogeneity, or little transparency in presenting excluded studies. Third, although we evaluated an increase in a given exposure and the corresponding increased risk for a given mental health outcome, we did not assume that a reduction in the same exposure automatically corresponds to a proportional decrease in that risk. Indeed, our evidence does not contradict the fact that, for example, exposure to extreme cold may also worsen mental health outcomes, as described in Northern European countries[105].

Fourth, although we analyzed specific associations, the exposures considered are not independent in the real world, and tend to co-occur. Therefore, our results cannot provide information on the interaction and interdependence between different exposures. Fifth, some associations may be spurious or mediated by external factors not included in the analysis, such as the age, sex, or socioeconomic distribution of the population considered. Finally, association does not mean causation. Future research may better investigate associations for which we found no or weak evidence, investigate non-linear relationships, and explore multiple environmental exposures simultaneously.

In conclusion, this umbrella review confirms that air pollution and climate change represent intertwined elements of the main global crisis of our time. The study extends the vast list of adverse effects of exposures to air pollution and climate change hazards on physical health by indicating that they are also a threat to global mental health. We quantified for the first time the negative impact that these exposures can exert on mental health worldwide, summarizing evidence-based associations that can inform future research and population health actions. Notably, while the magnitude of most class I or II associations discussed above is small, they extend to the entire world population, and are therefore likely to have a substantial impact.

Our findings can be used to inform educational and public awareness campaigns on the impact of air pollution and climate change hazards on mental health, and to ensure public participation in programmes and information access on the issue. As we are living in a time that many authors refer to as the "Anthropocene" (i.e., the geological epoch dating from the commencement of significant human impact on earth's ecosystems, including anthropogenic air pollution and climate change[106]), education is essential to encourage people to change their attitudes and behaviors and make informed decisions.

Widespread literacy on the impact of air pollution and climate change on mental health can empower all people and especially further motivate youth to take action[107]. Being aware of the available evidence and the associated actionable behaviors may also mitigate currently emerging pathological fears (e.g., *eco-anxiety*, *solastalgia*, or *ecological grief*)[10-12].

The current findings may also directly inform policy makers and institutions in order to better incorporate mental health as a core outcome in relevant policies. While mental health has recently received more attention in the context of environmental policies, this is still not enough. For example, initiatives such as the Lancet Countdown on Health and Climate Change, which aims to maintain an updatable monitoring system on climate change and human health, recognize that their system is currently limited when it comes to the impact of climate change on mental health [108]. Similarly, the WHO Policy Brief on Mental Health and Climate Change 2022[2] acknowledged that countries are not sufficiently considering mental health in their response to the climate emergency. Another report produced in the lead-up to the 2023 Climate Change Conference by the WHO highlighted that mental health considerations remain largely absent from country commitments to meeting the Paris Agreement[109]. We hope that our findings may represent a reference point for the next generation of climate change policies and research.

As the urgency for action on air pollution and climate change increases, researching the specific factors modulating the associations outlined in this umbrella review becomes crucial. Future research should facilitate a closer interdisciplinary cross-fertilization of environmental research and clinical psychiatry. A pivotal area of future research may include studies addressing the potential benefits of preventive approaches that target environmental exposures to improve physical and mental health outcomes conjointly. This umbrella review provides an initial evidence-based set of actionable targets that future interventional studies could empirically investigate.

Overall, the evidence-based associations identified here emphasize the need for collaborative, interdisciplinary efforts to develop and implement strategies that map and mitigate the effects of air pollution and climate change, and proactively protect mental health globally. This umbrella review calls for an urgent population-level response, inviting policy makers, health professionals, and the public to prioritize and invest in initiatives that address the intersection of air pollution and climate change with mental health, in order to create the conditions for a more resilient and sustainable future.

ACKNOWLEDGEMENTS

This work was supported by NextGenerationEU (NGEU) and funded by the Italian Ministry of University and Research, National Recovery and Resilience Plan, project MNESYS (PE0000006). J. Radua is supported by the Spanish Ministry of Science and Innovation (PI22/00261), the AXA Research Fund, EIT Health, and the CERCA Program. G. Fico's work is supported by a fellowship from "La Caixa" Foundation. E. Vieta is supported by the Spanish Ministry of Science and Innovation (PI21/00787); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2021-SGR-01358); the CERCA Programme, Generalitat de Catalunya; La Marató-TV3 Foundation; and the European Union Horizon 2020 Research and Innovation Program (H2020-EU.3.1.1 and H2020-EU.3.1.3). J. Radua and M. De Prisco contributed equally to this work. Supplementary information on this study is available at https://imardgroup.com/air_pollution_and_climate_change.

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DOI:10.1002/wps.21219

Algorithm-based modular psychotherapy vs. cognitive-behavioral therapy for patients with depression, psychiatric comorbidities and early trauma: a proof-of-concept randomized controlled trial

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Effect sizes of psychotherapies currently stagnate at a low-to-moderate level. Personalizing psychotherapy by algorithm-based modular procedures promises improved outcomes, greater flexibility, and a better fit between research and practice. However, evidence for the feasibility and efficacy of modular-based psychotherapy, using a personalized treatment algorithm, is lacking. This proof-of-concept randomized controlled trial was conducted in 70 adult outpatients with a primary DSM-5 diagnosis of major depressive disorder, a score higher than 18 on the 24-item Hamilton Rating Scale for Depression (HRSD-24), at least one comorbid psychiatric diagnosis according to the Structured Clinical Interview for DSM-5 (SCID-5), a history of at least "moderate to severe" childhood maltreatment on at least one domain of the Childhood Trauma Questionnaire (CTQ), and exceeding the cut-off value on at least one of three measures of early trauma-related transdiagnostic mechanisms: the Rejection Sensitivity Questionnaire (RSQ), the Interpersonal Reactivity Index (IRI), and the Difficulties in Emotion Regulation Scale-16 (DERS-16). Patients were randomized to 20 sessions of either standard cognitive-behavioral therapy alone (CBT) or CBT plus transdiagnostic modules according to a mechanism-based treatment algorithm (MoBa), over 16 weeks. We aimed to assess the feasibility of MoBa, and to compare MoBa vs. CBT with respect to participants' and therapists' overall satisfaction and ratings of therapeutic alliance (using the Working Alliance Inventory - Short Revised, WAI-SR), efficacy, impact on early trauma-related transdiagnostic mechanisms, and safety. The primary outcome for efficacy was the HRSD-24 score at post-treatment. Secondary outcomes included, among others, the rate of response (defined as a reduction of the HRSD-24 score by at least 50% from baseline and a score <16 at post-treatment), the rate of remission (defined as a HRSD-24 score ≤8 at post-treatment), and improvements in early trauma-related mechanisms of social threat response, hyperarousal, and social processes/empathy. We found no difficulties in the selection of the transdiagnostic modules in the individual patients, applying the above-mentioned cut-offs, and in the implementation of MoBa. Both participants and therapists reported higher overall satisfaction and had higher WAI-SR ratings with MoBa than CBT. Both approaches led to major reductions of depressive symptoms at post-treatment, with a non-significant superiority of MoBa over CBT. Patients randomized to MoBa were nearly three times as likely to experience remission at the end of therapy (29.4% vs. 11.4%; odds ratio, OR = 3.2, 95% CI: 0.9-11.6). Among mechanism-based outcomes, MoBa patients showed a significantly higher post-treatment effect on social processes/empathy (p<0.05) compared to CBT patients, who presented an exacerbation on this domain at post-treatment. Substantially less adverse events were reported for MoBa compared to CBT. These results suggest the feasibility and acceptability of an algorithm-based modular psychotherapy complementing CBT in depressed patients with psychiatric comorbidities and early trauma. While initial evidence of efficacy was observed, potential clinical advantages and interindividual heterogeneity in treatment outcomes will have to be investigated in fully powered confirmation trials.

Key words: Depression, early trauma, algorithm-based modular psychotherapy, mechanism-based treatment, cognitive-behavioral therapy, transdiagnostic treatment modules, trauma-related mechanisms, social processes, empathy

(World Psychiatry 2024;23:257–266)

In more than seven decades of research, psychotherapy has come a long way in proving its effects in treating mental health problems. Much research was stimulated by the development of disorder-specific approaches, particularly in the field of cognitive-behavioral therapy (CBT). However, this continuing evolution has not been paralleled by improved treatment outcomes.

Most evidence-based psychotherapy protocols are based on single-disorder specific manuals, disregarding common psychiatric comorbidities, transdiagnostic vulnerability factors such as early trauma, and the high phenomenological heterogeneity among patients. This mismatch between available disorder-specific protocols and individual patient characteristics diminishes treatment effects and may be one reason for the limited application of evidence-based psychotherapies in clinical practice.

Effect sizes of psychotherapies in general are currently stagnating at a low-to-moderate level. In the field of depression, a minimum of 50% of patients do not respond, with approximately two-thirds not achieving remission with first-line treatment[1], even when the procedure is in accordance with treatment guidelines[2,3].

Fueled by growing criticism that disorder-specific manuals fail to address an individual's complexity of transdiagnostic dysfunctional mechanisms and processes, research paradigms are currently shifting toward personalization of psychotherapy[4-6]. By taking differential treatment effects and interindividual differences into account, personalized psychotherapy could yield greater flexibility, improved outcomes, and a better fit between research and practice.

Within this movement, several distinct approaches have emerged recently. One such pathway to achieve personalization is modular therapy[7-10]. In contrast to conventional treatment protocols, modular approaches provide clinicians with an evidence-based toolbox, allowing to integrate treatment modules systematically, as independent but combinable sets of functional units. By tailoring module selection and application to the specific characteristics and needs of each patient, modular therapy promises higher acceptance by patients and therapists as well as better treatment outcomes[11].

Modularity as a fundamental treatment principle was established two decades ago and has been primarily researched in children and adolescents[7,12]. In adults, several feasibility trials with modular interventions have recently been conducted for a variety of mental health problems, with encouraging results[13-17]. However, up to now, there has been little information on the decision criteria used to select interventions. Notably, programs have not applied algorithms to choose the modules according to patients' characteristics in order to systematically personalize the treatment procedure.

Only one contemporary study provides initial evidence for the feasibility of statistical decision-making algorithms to guide mental health care[18]. However, the efficacy cannot be clearly assessed, as only pre-post results from an uncontrolled open trial in community college students are available to date[19].

The present study is the first to investigate algorithm-based modular psychotherapy for adult patients in an observer-blinded, randomized controlled trial. To represent a difficult-to-treat sample regularly seen in clinical practice, patients with a DSM-5 diagnosis of major depressive disorder, a score higher than 18 on the 24-item Hamilton Rating Scale for Depression (HRSD-24)[20], at least one psychiatric comorbidity, a history of at least "moderate to severe" childhood maltreatment, and disturbed early trauma-related transdiagnostic mechanisms according to Research Domain Criteria (RDoC)[21], were included.

The aim of the study was to evaluate the feasibility and acceptability, and to provide preliminary evidence for the efficacy of modular-based psychotherapy (MoBa) using a personalized treatment algorithm. This algorithm was derived from empirical evidence on the shared mechanisms underlying mental disorders after early trauma. These include overactivation of the fear/threat system, and dysfunctions of the arousal/affect regulation and social cognition systems[22-24].

The primary outcome for efficacy was the HRSD-24 score at the end of treatment. Secondary outcomes included, among others, the response and remission rate, and improvements in the early trauma-related mechanisms of social threat response, hyperarousal, and social processes/empathy.

METHODS

Study design and participants

In this parallel-arm, observer-blinded, randomized controlled trial (RCT), 70 early-traumatized outpatients with depression and psychiatric comorbidities were recruited at two German university psychiatric centers.

Eligible patients were 18-65 years old; had a primary DSM-5 diagnosis of major depressive disorder ascertained by the Structured Clinical Interview for DSM-5 (SCID-5)[25]; had a score higher than 18 on the HRSD-24[20]; had at least one comorbid psychiatric diagnosis according to the SCID-5; had a history of at least "moderate to severe" childhood maltreatment on at least one domain of the Childhood Trauma Questionnaire (CTQ)[26] (i.e., emotional neglect, emotional abuse, physical neglect, physical abuse, or sexual abuse); and exceeded the cut-off value on at least one of three measures of early trauma-related transdiagnostic mechanisms[23,27], i.e., a score ≥9.88 on the Rejection Sensitivity Questionnaire (RSQ)[28]; a score <45 on the Interpersonal Reactivity Index (IRI)[29], or a score ≥55.73 on the Difficulties in Emotion Regulation Scale-16 (DERS-16)[30].

Exclusion criteria were: an acute risk of suicide; another psychiatric disorder as the primary diagnosis; fulfilling diagnostic criteria for schizophrenia, bipolar I disorder, neurocognitive disorder, or substance use disorder during the last 6 months; a diagnosis of antisocial personality disorder or more than three traits of borderline personality disorder according to the Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5 PD)[31]; severe cognitive impairment; a serious medical condition (interfering with participation in therapy sessions); other ongoing psychotherapy or psychotropic medication, except antidepressant and/or sleep-inducing treatment, if stable for at least 3 weeks (4 weeks for fluoxetine). The selective use of a benzodiazepine as rescue medication on-demand for a maximum of 2 weeks was permitted, while the continuous intake of a benzodiazepine was not allowed[32].

The study protocol was approved by the independent Ethics Committees of the University of Freiburg (reference no. 414/20) and the University of Heidelberg (reference no. S-762/2020). The trial was preregistered at the German Clinical Trials Register (registration no. DRKS00022093). All participants provided written informed consent.

Randomization, masking and monitoring

Randomization was performed, stratified by site, in blocks of variable length in a ratio of 1:1. The block lengths were documented separately and not disclosed to the sites. All clinical interviews and outcome assessments were conducted by raters who were blinded to the treatment arm allocation.

The raters were centrally trained and certified in the assessment of clinician-rated outcomes, and inter-rater reliability was ensured as part of the training process. The sites implemented procedures to maintain rater blinding to treatment assignment by informing and reminding patients, at each visit, not to mention their treatment condition or related content to the raters. In addition, the raters and the study therapists were placed at different physical locations. Therapists refrained from any conversation about any aspects of individual treatments with the raters. On-site data monitoring was regularly conducted by clinical monitors from the Clinical Trials Unit Freiburg.

Interventions

The interventions included 20 manual-based individual sessions of CBT or MoBa over 16 weeks (twice weekly in weeks 1-4, once per week in weeks 5-16).

The CBT condition followed the German standard CBT manual for depression[33], including the following elements: building a therapeutic alliance, psychoeducation, behavior activation, cognitive restructuring, and strategies for maintenance and relapse prevention.

The MoBa condition included CBT as described above, complemented by at least one of three selected modules, which addressed disturbed mechanisms associated with early interpersonal traumatization.

Module 1 addressed the negative valence system (according to RDoC[21]) and the social threat response system, with the goal to reduce avoidance behavior. It used elements of the cognitive behavioral analysis system of psychotherapy (CBASP)[34,35], a method tailored for the treatment of early-onset chronically depressed patients, usually with a trauma history. The CBASP elements included in the module were the "significant other history" with a derived transference hypothesis, the "interpersonal discrimination exercise", and the therapist's "contingent personal reactivity" (see also supplementary information). The questionnaire assessing the domains covered by this module was the RSQ[28].

Module 2 addressed the system for social processes (according to RDoC[21]), with the goal of enhancing perception and understanding of self and others, empathy and social communication. It used strategies of mentalization-based therapy (MBT)[36]. This included modelling and teaching mentalization, so that the patient could learn to "read" others' behavior and was thereby reconnected to his/her social environment, fostering his/her social competence (see also supplementary information). The questionnaire assessing the domains covered by this module was the IRI[29].

Module 3 addressed the arousal system (according to RDoC[21]), with the goal of reducing hyperarousal. It used the emotion awareness and regulation techniques of mindfulness-based cognitive therapy (MBCT)[37]. This included mindfulness exercises focusing on: observing non-judgmentally internal and external stimuli; shifting attention away from trauma-related inner "movies"; and monitoring skills to overcome hyperarousal or being run over by one's emotions (see also supplementary information). The questionnaire assessing the domains covered by this module was the DERS-16[30].

The study therapists, who were clinical psychologists with a CBT background, received a formal training in both manualized interventions by experts of the respective fields. Adherence to the manuals was assured by continuous supervision. All therapy sessions were video-recorded, and randomly selected sequences were watched by the supervisors. In addition, adherence was checked by asking therapists to fill out a Therapeutic Element Checklist (TEC) (see supplementary information) immediately after each session. Supervisors reviewed the TECs regularly.

Outcomes and assessments

We investigated the feasibility of the selection of the therapeutic modules in the individual patients – applying the above-mentioned cut-off values for measures of early trauma-related transdiagnostic mechanisms – and of the implementation of MoBa. Participants' and therapists' overall satisfaction with MoBa and CBT was assessed by the TEC after each session. The therapeutic alliance was evaluated by participants and therapists using the Working Alliance Inventory - Short Revised (WAI-SR)[38] at the end of treatment. The WAI-SR assesses three key aspects of the therapeutic alliance: agreement on tasks of therapy, agreements on goals of therapy, and development of an affective bond.

The primary efficacy outcome was defined *a priori* as the HRSD-24[20] score at the end of treatment measured by blind, independent raters. Secondary outcomes included the rate of response (defined as a reduction of the HRSD-24 score by at least 50% from baseline and a score <16 at post-treatment), and the rate of remission (defined as a HRSD-24 score ≤8 at post-treatment).

Further secondary outcomes comprised: a) self-rated depressive and anxiety symptoms, as assessed by the Beck Depression Inventory-II (BDI-II)[39] and the Beck Anxiety Inventory (BAI)[40]; b) improvements in the early trauma-related mechanisms of social threat response, hyperarousal, and social processes/empathy, as assessed by the RSQ[28], the DERS-16[30], and the IRI[29], respectively; c) improvements in clinician-rated social and occupational functioning, as assessed by the Social and Occupational Functioning Assessment Scale (SOFAS)[41], and in self-rated quality of life, as assessed by the World Health Organization Quality of Life - Brief Version (WHOQOL-BREF)[42].

We also assessed the deterioration rate, in both treatment groups, using the reliable change index based on the variance and reliability of the HRSD-24 score at baseline and post-treatment.

Adverse events and serious adverse events were recorded for the entire treatment duration, using a well-established checklist[43]. Adverse events were defined as any unfavorable and unintended sign, symptom or disease, whether or not considered to be related to the treatment (this included worsening of symptoms, occurrence of new symptoms, occurrence of passive suicidal thoughts, active suicidal intentions or plans, problems in the patient-therapist relationship, private problems, occupational problems, or other medical conditions). Serious adverse events were defined as any medical event that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability or incapacity (this included any medical condition that might require medical or surgical intervention to prevent one of the above outcomes, including suicide attempts).

Statistical analyses

Due to the exploratory nature of the trial and the lack of comparable studies, no formal sample size calculation was possible[32]. Following Billingham et al[44], a sample size of 30 patients per group was regarded as reasonable, resulting in a total of 60 patients. Non-compliance and/or dropout of patients after randomization was assumed to be at most 14%. Therefore, 70 patients were randomized, split in the two treatment groups for each of the two participating centers.

The primary efficacy analysis was performed according to the intention-to-treat principle and was based on the full analysis set. This included all randomized patients, who were analyzed as belonging to their randomized arm, regardless of whether they refused therapy, or whether other protocol deviations were known. The effects of CBT and MoBa with respect to the HRSD-24 post-treatment (primary endpoint) were estimated within a linear regression model and the two-sided 95% confidence interval (CI). The model included treatment and study center as independent variables, as well as baseline HRSD-24 score.

Secondary endpoints were analyzed descriptively in a similar fashion, using regression models as appropriate for the respective type of data. Treatment effects were calculated with corresponding two-sided 95% CIs.

The primary and secondary endpoints were also evaluated in linear regression models as described above, but additionally adjusting for the depression type (episodic depressive disorder vs. persistent depressive disorder or dysthymic syndrome with superimposed major depressive episodes).

RESULTS

A total of 119 patients were screened for eligibility at both centers from December 2019 to March 2022, of whom 70 were included and randomized to MoBa or CBT. One patient in the MoBa group discontinued the study due to relocation. Four patients (three in MoBa, one in CBT) dropped out after less than 17 sessions. All patients were included in the intention-to-treat analysis (see Figure 1).

Sample characteristics

Demographic, historical and clinical baseline characteristics of the participants in the intention-to-treat sample are shown in Table 1. The mean age was 38.9±13.2 years in the MoBa group and

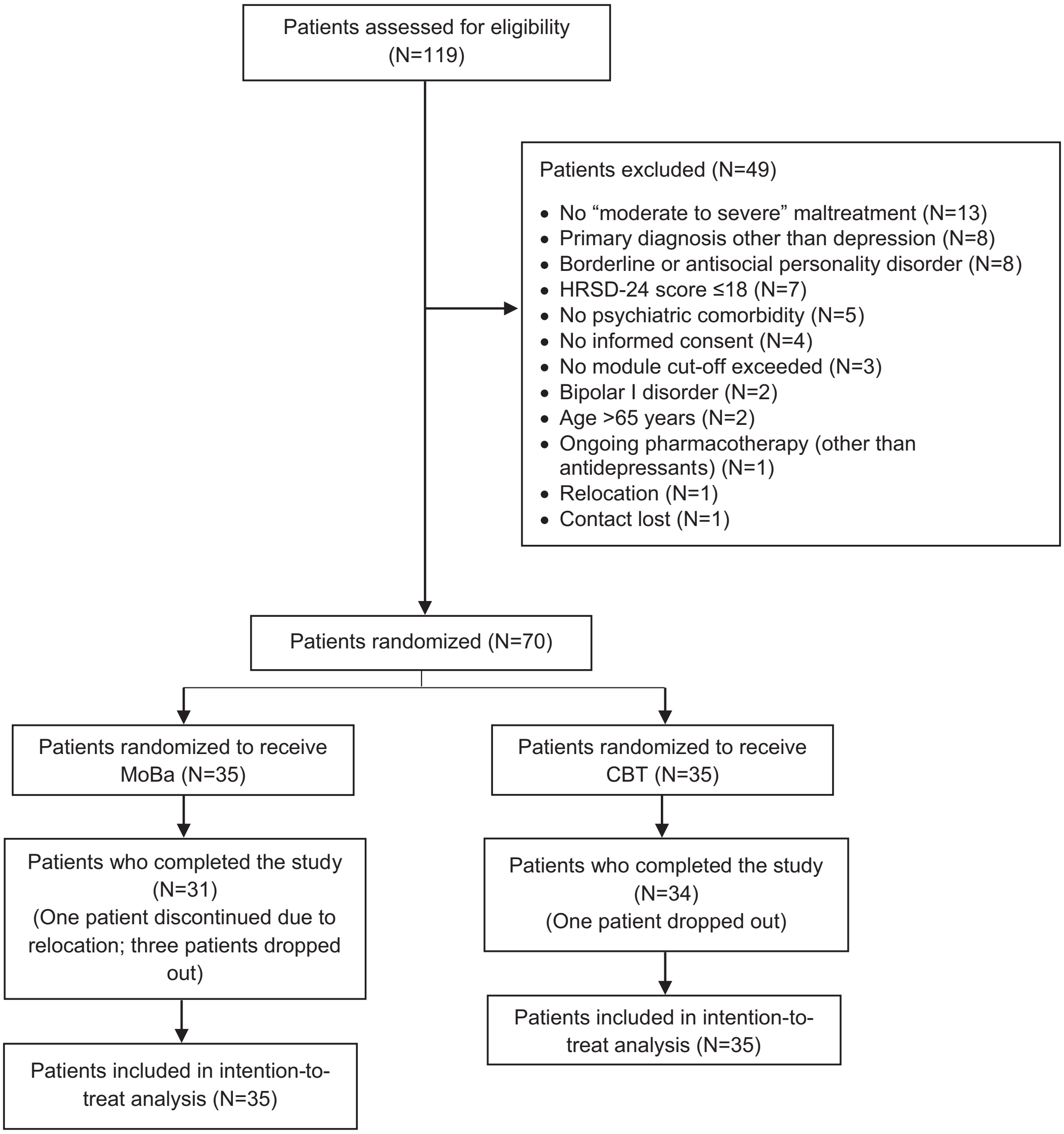


Figure 1 Study flow chart. MoBa – algorithm-based modular psychotherapy, CBT – standard cognitive-behavioral therapy, HRSD-24 – 24-item Hamilton Rating Scale for Depression.

Table 1 Demographic, historical and clinical baseline characteristics of participants in the study

	MoBa (N=35)	CBT (N=35)
Age (years), mean±SD	38.9±13.2	44.4±15.3
Gender, N (%)		
Female	25 (71.4)	24 (68.6)
Male	10 (28.6)	10 (28.6)
Non-binary	0	1 (2.9)
Marital status, N (%)		
Single	15 (42.9)	19 (55.9)
Married/registered partnership	7 (20.0)	5 (14.7)
Permanent partnership	10 (28.6)	1 (2.9)
Divorced/separated	3 (8.6)	9 (26.5)
Widowed	0	0
Educational level, N (%)		
Low (less than 9 years)	2 (5.7)	2 (5.7)
Medium (10-11 years)	7 (20.0)	11 (31.4)
High (12+ years)	26 (74.3)	22 (62.9)
Employment, N (%)		
Full-time	5 (15.2)	4 (11.8)
Part-time	7 (21.2)	9 (26.5)
Marginally/irregularly employed	8 (24.2)	3 (8.8)
In training	2 (6.1)	2 (5.9)
Not employed	11 (33.3)	16 (47.1)
Depression type, N (%)		
Episodic depressive disorder	11 (31.4)	20 (57.1)
Persistent depressive disorder	12 (34.3)	7 (20.0)
Dysthymic syndrome with superimposed major depressive episodes	12 (34.3)	8 (22.9)
Age at first depressive episode (years), mean±SD	20.1±11.4	20.0±9.3
Family history of mental disorder, N (%)	27 (77.1)	23 (65.7)
Comorbid psychiatric diagnoses (number), mean±SD	1.9±0.9	1.9±1.1
Childhood maltreatment in individual CTQ domains, N (%)		
Emotional neglect	32 (91.4)	29 (82.9)
Emotional abuse	25 (71.4)	27 (77.1)
Physical neglect	14 (40.0)	11 (31.4)
Physical abuse	10 (28.6)	10 (28.6)
Sexual abuse	11 (31.4)	7 (20.6)
CTQ domains on which maltreatment was reported, N (%)		
One	8 (22.9)	10 (28.6)
Two	8 (22.9)	12 (34.3)
Three	10 (28.6)	6 (17.1)
Four	7 (20.0)	3 (8.6)
Five	2 (5.7)	4 (11.4)
CTQ domains on which maltreatment was reported, mean±SD	2.6±1.2	2.4±1.3
Previous suicide attempts, N (%)		
None	23 (65.7)	29 (82.9)
One	9 (25.7)	2 (5.7)
At least two	3 (8.6)	4 (11.4)
Previous inpatient psychiatric treatment, N (%)		
Yes	16 (45.7)	11 (31.4)
No	19 (54.3)	24 (68.6)
Current HRSD-24 score, mean±SD	26.3±4.7	27.6±7.3
Current physical comorbidities, N (%)	20 (57.1)	15 (42.9)
Currently receiving psychopharmacological treatment, N (%)	21 (60.0)	25 (71.4)

MoBa – algorithm-based modular psychotherapy, CBT – standard cognitive-behavioral therapy, HRSD-24 – 24-item Hamilton Rating Sale for Depression, CTQ – Childhood Trauma Questionnaire

44.4±15.3 years in the CBT sample. The proportion of females was, respectively, 71.4% and 68.6%. Most patients were single (42.9% and 55.9%) and not employed (33.3% and 47.1%) in both groups.

Patients in the MoBa group had more frequently a diagnosis of persistent depressive disorder (34.3% vs. 20.0%) or dysthymic syndrome with superimposed major depressive episodes (34.3% vs. 22.9%). The current mean HRSD-24 score was 26.3±4.7 in MoBa and 27.6±7.3 in CBT patients. The mean duration of the current depressive condition was 204 days in MoBa and 142 days in CBT patients. Patients in the MoBa arm reported twice as many past suicide attempts prior to treatment (34.3% vs. 17.1%) and were more likely to present current physical comorbidities (57.1% vs. 42.9%).

The mean number of comorbid psychiatric diagnoses was 1.9 in both groups (range: 1-5). Anxiety disorders were the most frequent comorbid diagnoses (27.1% of patients were diagnosed with generalized anxiety disorder, 22.9% with social anxiety disorder, 14.3% with panic disorder, 14.3% with specific phobia, and 7.1% with agoraphobia). Furthermore, 25.7% of patients received a comorbid diagnosis of personality disorder (20.0% avoidant, 2.9% dependent, 1.4% narcissistic, and 1.4% obsessive-compulsive); 21.4% had comorbid post-traumatic stress disorder; 15.7% attention-deficit/hyperactivity disorder (ADHD); 11.4% obsessive-compulsive or related disorders; 7.1% sleep-wake disorders; 5.8% feeding or eating disorders; 4.3% premenstrual dysphoric disorder; and 4.3% unspecified somatic symptom and related disorders.

Childhood maltreatment (at least "moderate to severe") was reported in a mean number of CTQ domains of 2.6±1.2 for the MoBa and 2.4±1.3 for the CBT group. Overall, 87.1% of patients experienced emotional neglect (35.7% "moderate to severe", 51.4%

"severe to extreme"); 74.3% emotional abuse (22.9% "moderate to severe", 51.4% "severe to extreme"); 35.7% physical neglect (15.7% "moderate to severe", 20.0% "severe to extreme"); 28.6% physical abuse (10.0% "moderate to severe", 18.6% "severe to extreme"); and 26.1% sexual abuse (13.0% "moderate to severe", 13.0% "severe to extreme").

The proportion of patients currently receiving psychopharmacological treatment was 60.0% in the MoBa and 71.4% in the CBT group. Overall, 65.7% of patients were receiving medication. Of these, 17.1% reported the stable use of selective serotonin reuptake inhibitors, 12.9% of non-selective monoamine reuptake inhibitors, 42.9% of other antidepressants. The proportion of patients with a history of inpatient psychiatric treatment was 45.7% in the MoBa and 31.4% in the CBT sample.

Module allocation and treatment implementation

In the MoBa group, treatment modules were selected in the individual patients according to a systematic algorithm applying the above-mentioned cut-off values for measures of early trauma-related transdiagnostic mechanisms. Among patients randomized to this group, 17.1% received only the Module 1; 11.4% only the Module 2; 14.3% the Modules 1 and 2; 31.4% the Modules 1 and 3; 2.9% the Modules 2 and 3; and 22.9% the Modules 1, 2 and 3. No patient received only the Module 3 (see Figure 2).

Overall, patients received a mean of 17.3±4.0 therapy sessions. In the MoBa group, the mean time in a session applying CBT elements was 43.2%. If CBASP and/or mentalization and/or mindfulness elements were part of the modular intervention, the mean time spent on each of these elements was, respectively, 50.5%, 45.9%, and 33.9%.

Feasibility and acceptability

We found no difficulties in the selection of the therapeutic modules in the individual patients – by applying the above-mentioned cut-off values for measures of early trauma-related transdiagnostic mechanisms – and in the implementation of MoBa.

Therapists recorded high or very high satisfaction more frequently after a modular therapy session than after a CBT session (92.8% vs. 82.9%). The same applied to patients (82.9% vs. 74.3%). Difficulties in the patient-therapist relationship were reported by 5.7% of patients in the MoBa and 11.4% in the CBT group. The therapeutic alliance was rated as better by both therapists and participants in the MoBa vs. the CBT group on all three factors: agreement on tasks of therapy (mean difference: 0.24 for therapists and 0.22 for patients); agreement on goals of therapy (0.24 and 0.02); and affective bond (0.05 and 0.16), although no difference was statistically significant.

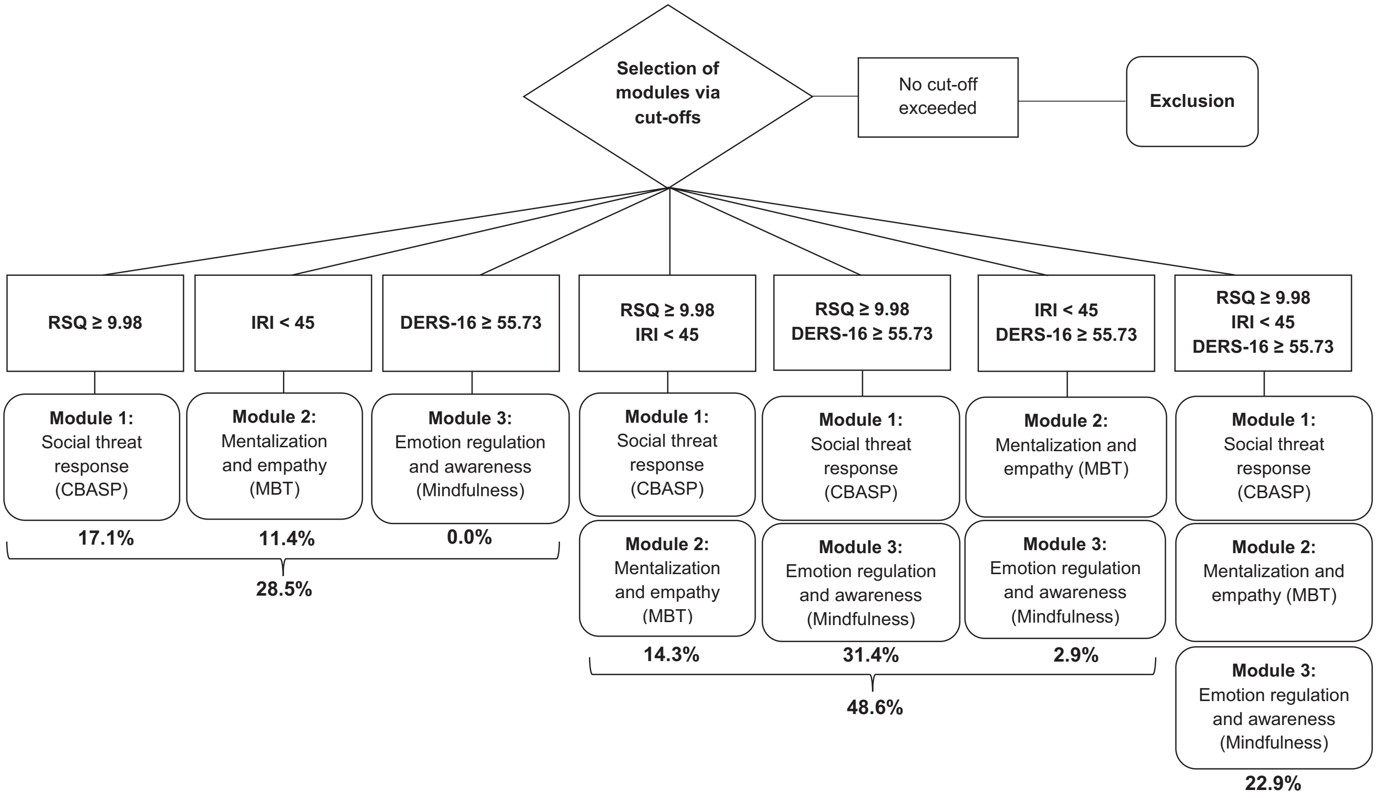
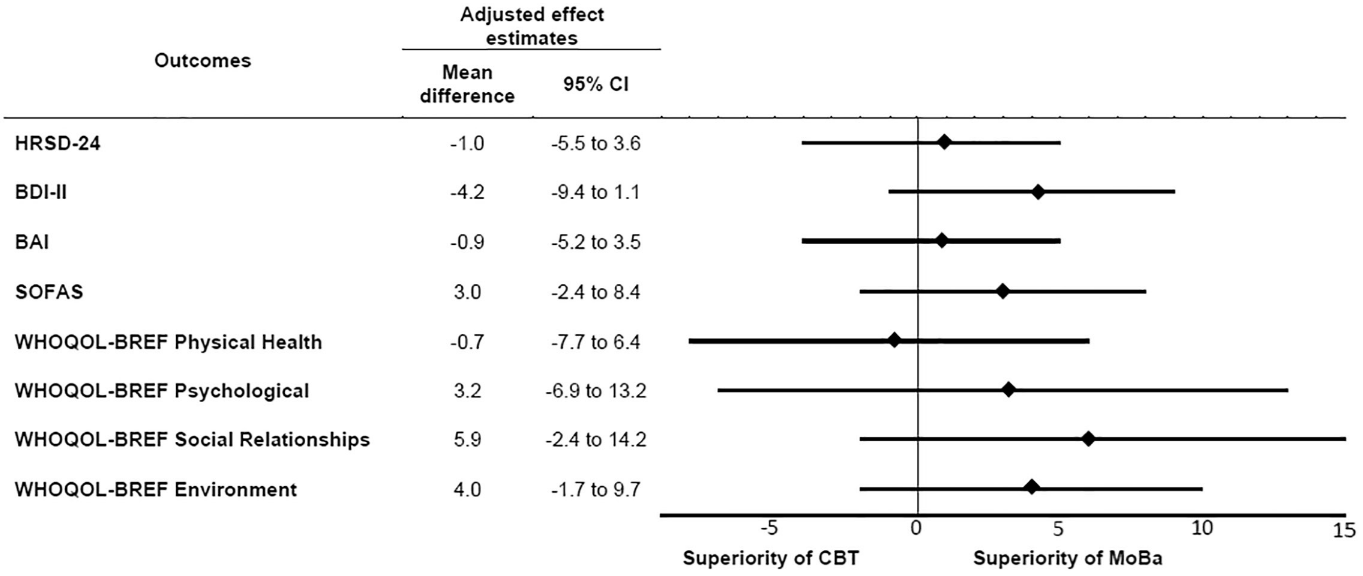


Figure 2 Selection of modules according to the evidence-based algorithm. RSQ – Rejection Sensitivity Questionnaire, IRI – Interpersonal Reactivity Index, DERS-16 – Difficulties in Emotion Regulation Scale-16, CBASP – cognitive behavioral analysis system of psychotherapy, MBT – mentalization-based therapy.



Outcomes	Adjusted effect estimates: Mean difference	Adjusted effect estimates: 95% CI
HRSD-24	-1.0	-5.5 to 3.6
BDI-II	-4.2	-9.4 to 1.1
BAI	-0.9	-5.2 to 3.5
SOFAS	3.0	-2.4 to 8.4
WHOQOL-BREF Physical Health	-0.7	-7.7 to 6.4
WHOQOL-BREF Psychological	3.2	-6.9 to 13.2
WHOQOL-BREF Social Relationships	5.9	-2.4 to 14.2
WHOQOL-BREF Environment	4.0	-1.7 to 9.7

Figure 3 Estimated mean differences between algorithm-based modular psychotherapy (MoBa) and standard cognitive-behavioral therapy (CBT) for measures of clinical efficacy, adjusted for depression type. HRSD-24 – 24-item Hamilton Rating Scale for Depression, BDI-II – Beck Depression Inventory-II, BAI – Beck Anxiety Inventory, SOFAS – Social and Occupational Functioning Assessment Scale, WHOQOL-BREF – World Health Organization Quality of Life - Brief Version.

Patients in the MoBa group completed homework more often than in the CBT group (89.6% vs. 71.0%). Therapists reported more time problems in MoBa compared to CBT sessions (31.4% vs. 18.6%).

Efficacy

After 16 weeks of treatment, the mean HRSD-24 score was 17.2 (95% CI: 14.1-20.4) in the MoBa group and 17.4 (95% CI: 14.3-20.5) in the CBT group. Using the linear regression model, we found an estimated mean difference of –0.2 (95% CI: –4.6 to 4.2). After adjusting for the depression type, the estimated mean difference was –1.0 (95% CI: –5.5 to 3.6). So, concerning the primary outcome, there was a non-significant superiority of MoBa over CBT (see Figure 3).

The response rate was slightly higher in the MoBa than the CBT group (35.3% vs. 31.4%; OR=1.2, 95% CI: 0.4-3.2). However, MoBa patients were nearly three times as likely to experience remission at the end of therapy (29.4% vs. 11.4%, OR=3.2, 95% CI: 0.9-11.6).

Secondary efficacy outcomes showed a non-significant superiority of MoBa over CBT, with a mean difference (after adjusting for the depression type) of –4.2 (95% CI: –9.4 to 1.1) for BDI-II, of –0.9 (95% CI: –5.2 to 3.5) for BAI, of 3.0 (95% CI: –2.4 to 8.4) for SOFAS, of 3.2 (95% CI: –6.9 to 13.2) for WHOQOL-BREF Psychological, of 5.9 (95% CI: –2.4 to 14.2) for WHOQOL-BREF Social Relationships, and of 4.0 (95% CI: –1.7 to 9.7) for WHOQOL-BREF Environment. The only exception was WHOQOL-BREF Physical Health, which showed a non-significant superiority of CBT (mean difference: –0.7, 95% CI: –7.7 to 6.4) (see Figure 3).

Among mechanism-based outcomes, MoBa patients showed a significantly higher post-treatment effect on social processes/empathy after adjusting for the depression type, with an estimated mean difference of 1.9 (95% CI: 0.0-3.8, $p<0.05$) in the IRI score compared with the CBT group. This latter group actually showed an exacerbation on this domain at post-treatment (see Table 2). The adjusted effect estimates also favored MoBa for the other two mechanism-based outcomes, but not at a statistically significant level: the mean difference, after adjusting for the depression type, was 1.6 (95% CI: –0.7 to 3.9) for the RSQ score, and 1.8 (95% CI: –4.3 to 7.9) for the DERS-16 score (see Table 2).

Overall, 5 of 69 patients (7.2%) deteriorated during treatment, with a mean exacerbation of –6.6 (SD=0.5) HRSD-24 points. Of these, three patients had been randomized to MoBa and two to

Table 2 Estimated mean differences between algorithm-based modular psychotherapy (MoBa) and standard cognitive-behavioral therapy (CBT) for mechanism-based outcomes, adjusted for depression type

	MoBa		CBT		Adjusted effect estimates	
	N	Adjusted mean (SE)	N	Adjusted mean (SE)	Mean difference	95% CI
Rejection Sensitivity Questionnaire (RSQ)						
Baseline	35	16.0 (0.93)	35	15.3 (0.88)		
Post-treatment	34	12.2 (0.81)	33	10.6 (0.81)	1.6	–0.7 to 3.9
Interpersonal Reactivity Index (IRI)						
Baseline	35	44.1 (1.04)	35	43.4 (1.34)		
Post-treatment	34	45.0 (0.68)	35	43.1 (0.65)	**1.9**	**0.0 to 3.8**
Difficulties in Emotion Regulation Scale (DERS-16)						
Baseline	35	56.7 (1.95)	35	51.8 (1.92)		
Post-treatment	34	45.5 (2.18)	35	43.7 (2.09)	1.8	–4.3 to 7.9

The significant difference between MoBa and CBT ($p<0.05$) is highlighted in bold prints

CBT.

Safety

Overall, 44 adverse events occurred during the trial, including symptom exacerbation or occurrence of new symptoms in eight cases, passive suicidal thoughts in eight cases, and problems in the patient-therapist relationship in four cases. The number of adverse events was substantially lower in the MoBa group (15; 34.1%) than in the CBT group (29; 65.9%), corresponding to an average number of 0.43 events per MoBa patient, and 0.83 events per CBT patient. No severe adverse events were reported.

DISCUSSION

This is the first randomized controlled trial to investigate the feasibility, acceptability and efficacy of an algorithm-based selection of treatment modules complementing standard CBT. The algorithm was derived from a mechanistic model of the sequelae of early life adversity, and therapists were asked to select, in the individual patients, the appropriate modules on the basis of a baseline assessment of those sequelae.

In a highly burdened sample of early traumatized patients with mostly persistent or recurrent depression and psychiatric comorbidities, the modular approach proved highly acceptable. Both patients and therapists reported high or very high post-session satisfaction more frequently with MoBa than with CBT. The therapeutic alliance was rated as better by both patients and therapists in the MoBa vs. the CBT group regarding all its key elements (agreement on tasks of therapy, agreement on goals of therapy, and affective bond).

MoBa therapists reported more time pressure, very likely because of the challenge to integrate the additional modules within a small number of 20 sessions. On the other hand, patients in the MoBa group completed homework more often and reported less difficulties in their relationship to the therapist than those in the CBT group.

Very few of these severely affected patients dropped out or deteriorated. Patients receiving MoBa reported a substantially lower number of adverse events than those in the CBT group. No serious adverse event occurred.

The MoBa approach was associated with a superiority over standard CBT on both the primary (HRSD-24 score at post-treatment) and almost all of the secondary (self-rated depressive and anxiety symptoms, clinician-rated social and occupational functioning, self-rated quality of life) efficacy outcomes. However, no difference reached statistical significance, most likely due to the small sample size.

Patients in the modular treatment arm were nearly three times as likely to show post-treatment remission (29.4% vs. 11.4%, OR=3.2). This finding provides a preliminary support to the usefulness of a modular mechanism-based approach aimed to personalize psychotherapy[9,45], in order to address the substantial interindividual heterogeneity in treatment effects among depressed patients[46-52].

Our treatment algorithm was based on the baseline assessment of three early trauma-related transdiagnostic mechanisms: social threat response, hyperarousal, and social processes/empathy. There was a significant differential treatment effect regarding social processes/empathy, as MoBa patients reported pre-post improvements while CBT patients showed an exacerbation on this domain. Interestingly, the mentalizing module addressing this domain was the only one including elements not derived from a third-wave CBT, but from a psychodynamic approach[36]. The adjusted effect estimates also favored MoBa on the other two mechanism-based outcomes, although the difference did not reach a statistically significant level, again likely due to the small sample size.

Statistical analyses were limited to overall comparisons of MoBa vs. CBT, since tests comparing different modules were not sufficiently powered. While the modules were selected based on an evidence-based algorithm, the sequencing of the strategies within modules were based on the therapists' individual case conceptualizations. There is no reliable evidence to support a data-driven decision algorithm for sequencing as yet. However, monitoring and feedback systems have been reported to increase the efficacy of psychotherapies by further personalizing and adapting interventions to the patients' response[53,54]. These will be tested in a future confirmatory trial.

Since both interventions were provided by the same therapists, some degree of involuntary treatment diffusion might have occurred[55,56]. Therefore, separate therapists being trained in and delivering only one intervention will have to be used in the future to systematically prevent this effect.

Up to now, little is known about how interventions should be structured in modular psychotherapies[57]. Different from most practicing clinicians who follow eclectic treatment approaches according to their expertise and intuition[58], empirically based rules are needed to arrive at replicable treatment standards. This is the first study which applied a personalized decision-making principle of module selection based on an algorithm derived from a mechanistic model. It is notable that this model was informed by the RDoC approach, which does not happen frequently in clinical trials and practice.

Although MoBa randomized participants had characteristics associated with greater treatment resistance than those receiving standard CBT, the modular approach proved to be feasible, safe and effective, showing advantages related to patients' and therapists' satisfaction and several clinical outcomes. While this seems highly promising as a distinct pathway to achieve personalization, further evaluation will be needed in a fully powered confirmatory trial.

To account for the results of this proof-of-concept trial, an optimized design will have to incorporate more therapy sessions, include a monitoring system, and involve patients in standardized shared decision-making to sequence modules. In the future, a combination of theory- and data-based algorithms may be optimal, with machine learning analyses of actuarial data to build replicable processes and outputs.

ACKNOWLEDGEMENTS

This trial was funded by the German Research Foundation (grant no. SCHR443/16-

1), and the work was endorsed by the German Center for Mental Health (DZPG). The authors would like to thank the study team and all contributors to the trial, in particular the site project coordinator R. Bullenkamp; the study therapists N. Zehender, C. Breuninger, J. Hundertmark and F. Herrmann; and the module trainers S. Taubner and A. Külz. E. Schramm and M. Elsaesser contributed equally to this work. Supplementary information on this study is available at https://osf.io/spkx4.

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DOI:10.1002/wps.21204

Absolute and relative outcomes of psychotherapies for eight mental disorders: a systematic review and meta-analysis

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Psychotherapies are first-line treatments for most mental disorders, but their absolute outcomes (i.e., response and remission rates) are not well studied, despite the relevance of such information for health care users, providers and policy makers. We aimed to examine absolute and relative outcomes of psychotherapies across eight mental disorders: major depressive disorder (MDD), social anxiety disorder, panic disorder, generalized anxiety disorder (GAD), specific phobia, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and borderline personality disorder (BPD). We used a series of living systematic reviews included in the Metapsy initiative (www.metapsy.org), with a common strategy for literature search, inclusion of studies and extraction of data, and a common format for the analyses. Literature search was conducted in major bibliographical databases (PubMed, PsycINFO, Embase, and the Cochrane Register of Controlled Trials) up to January 1, 2023. We included randomized controlled trials comparing psychotherapies for any of the eight mental disorders, established by a diagnostic interview, with a control group (waitlist, care-as-usual, or pill placebo). We conducted random-effects model pairwise meta-analyses. The main outcome was the absolute rate of response (at least 50% symptom reduction between baseline and post-test) in the treatment and control conditions. Secondary outcomes included the relative risk (RR) of response, and the number needed to treat (NNT). Random-effects meta-analyses of the included 441 trials (33,881 patients) indicated modest response rates for psychotherapies: 0.42 (95% CI: 0.39-0.45) for MDD; 0.38 (95% CI: 0.33-0.43) for PTSD; 0.38 (95% CI: 0.30-0.47) for OCD; 0.38 (95% CI: 0.33-0.43) for panic disorder; 0.36 (95% CI: 0.30-0.42) for GAD; 0.32 (95% CI: 0.29-0.37) for social anxiety disorder; 0.32 (95% CI: 0.23-0.42) for specific phobia; and 0.24 (95% CI: 0.15-0.36) for BPD. Most sensitivity analyses broadly supported these findings. The RRs were significant for all disorders, except BPD. Our conclusion is that most psychotherapies for the eight mental disorders are effective compared with control conditions, but absolute response rates are modest. More effective treatments and interventions for those not responding to a first-line treatment are needed.

Key words: Psychotherapies, response rates, depression, social anxiety disorder, panic disorder, generalized anxiety disorder, specific phobia, post-traumatic stress disorder, obsessive-compulsive disorder, borderline personality disorder

(World Psychiatry 2024;23:267–275)

About 970 million people worldwide suffer from a mental disorder[1]. Depression and anxiety disorders are the most prevalent conditions, but the prevalence rates of other disorders – such as post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD) and borderline personality disorder (BPD) – are also remarkably high. For these disorders, evidence-based treatments are available, with psychotherapies being first-line interventions [2].

Treatment outcomes of psychotherapies are usually examined by continuous measures (i.e., mean scores on rating scales). Meta-analyses typically report outcomes as standardized mean differences (SMDs), which indicate the difference between an intervention and a control condition in terms of standard deviation units. Although this is a correct way of reporting outcomes, these effect sizes are difficult to interpret for patients, providers and policy makers[3,4].

Binary outcomes such as response (defined, in the case of depression, as a 50% symptom reduction between baseline and post-test) and remission (i.e., a state in which the individual has no more than minimal symptoms) are easier to interpret[5]. However, trials and meta-analyses typically report these outcomes by comparing the treatment with a control condition in terms of relative risks (RRs), odds ratios (ORs), or number needed to treat (NNT), i.e., how many patients need to be treated to have one more positive outcome compared to controls[6].

Absolute outcomes, in terms of response or remission rates of treatments, are typically not pooled in meta-analyses, because this would assume that these rates are comparable across trials, which may not be the case[7]. Such absolute outcomes are, however, essential for clinical decision-making. In other areas, for example in meta-analyses of prevalence rates of mental disorders, absolute rates are often pooled[8-10].

Hundreds of randomized controlled trials have examined the effects of psychotherapies, and meta-analyses have shown that these therapies are effective across a broad range of mental disorders, including major depressive disorder (MDD)[11,12], PTSD[13,14], OCD[15], BPD[16,17], and anxiety disorders[18-22]. Very few meta-analyses, however, have focused on more than one mental disorder, while a broader focus on multiple disorders can allow an assessment of the comparative "treatability" of these conditions.

This is also important because psychotherapies are compared with different types of control conditions, which can lead to differential effect sizes. For example, in the field of depression, it is well established that the use of waitlist as the control condition may overestimate the effects of treatments[23]. In anxiety disorders, almost all trials have used waitlist, and there are indications that care-as-usual control groups result in considerably smaller effect sizes[22]. In BPD, virtually all trials make use of care-as-usual control groups[16,17]. One advantage of examining absolute outcomes is that this is done separately for the treatment and control groups, so that a comparison between the relative "treatability" of mental disorders is not complicated by differences in control conditions.

In this meta-analytic study, we examined the absolute and relative outcomes of psychotherapies for eight major mental disorders: MDD, PTSD, OCD, BPD, panic disorder, generalized anxiety disorder (GAD), social anxiety disorder, and specific phobia. As primary outcome, we considered the absolute measure of response rate[24]. In the field of treatments for depression, response is often defined as a 50% symptom reduction[5]. In other fields, the definition of response is less clear. For example, in studies on anxiety disorders, a broad range of different definitions is used[25], and the same is true for PTSD[26]. In this meta-analysis, we used the same definition of response (number of patients with at least 50% symptom reduction between baseline and post-test, divided by the total number of patients) across all included mental disorders. This allows to have a comparable outcome across these different disorders, providing an indication of their relative "treatability". To the best of our knowledge, no previous meta-analysis has reported absolute outcomes across psychotherapies for a range of mental disorders.

METHODS

Search strategy and selection criteria

This meta-analysis was registered at the Open Science Framework (https://doi.org/10.17605/osf.io/rpw6g). We used a series of living systematic reviews included in the Metapsy project (www.metapsy.org), with a common strategy for search of literature, inclusion of studies and extraction of data, and a common format for the analyses. All included datasets are updated at least once per year (deadline for the current study: January 1, 2023).

Major bibliographical databases – including PubMed, PsycINFO, Embase, and the Cochrane Register of Controlled Trials – were searched by combining terms (index and text words) indicative of each of the mental disorders and psychotherapies, with filters for randomized controlled trials. Separate searches were conducted for MDD, PTSD, OCD and BPD. A combined search was performed for four anxiety disorders: panic disorder, GAD, social anxiety disorder, and specific phobia. Full search strings are presented in the supplementary information.

All identified records were screened by two researchers, and all records that could possibly meet inclusion criteria according to one of the researchers were retrieved in full text. The decision to include a study was also made by two independent researchers, and disagreements were resolved through consensus and, if needed, consultation with a third rater.

For the current meta-analysis, we included randomized controlled trials in which a psychotherapy[27] for adults with any of the eight mental disorders, as established by a diagnostic interview, was compared with a control group (waitlist, care-as-usual, or pill placebo). We excluded studies with other control conditions, those including participants based on self-report symptom measures; those on inpatients, children or adolescents; those examining unguided self-help interventions, and those with insufficient data to calculate the response rate.

Quality assessment and data extraction

The quality of the included trials was evaluated using the Cochrane Risk of Bias (RoB) assessment tool version 1 (for the dataset on MDD)[28] or version 2 (for the other seven datasets)[29]. We used four criteria of the RoB tool 1: sequence generation, concealment of allocation to conditions, prevention of knowledge of the allocated intervention, and dealing with incomplete outcome data. RoB tool 2 assessed the same domains in more detail, as well as whether analyses were pre-specified. We separated the trials in each of the eight datasets into two categories: low RoB and other. The definition of low RoB varied across the datasets (definitions are provided in Table 1). All assessments of RoB were conducted by two independent researchers, and disagreements were resolved through discussion with a third author.

We extracted several other characteristics of the trials and interventions: mean age of participants, proportion of women, whether the participants were recruited exclusively from clinical samples, type of psychotherapy (see supplementary information for definitions), treatment format, number of sessions, type of control condition, and country where the study was conducted.

Estimation of response rates

Treatment response was defined as the number of patients with at least 50% symptom reduction between baseline and post-test, divided by the total number of patients. For the calculation of the response rate, we used one outcome measure in each study. If multiple outcome measures were used, we selected the measure that was most frequently used.

Patients randomized but not included in the analyses of responders in the original reports were assumed to be non-responders and included in the main analyses to abide by the intention-to-treat principle. This was considered the most conservative estimate. We conducted sensitivity analyses in which we only included study completers, or all dropouts were considered responders.

We calculated response rates using a validated method using

Table 1 Overview of literature search and characteristics of included studies and interventions

	MDD	PAN	SAD	GAD	PHOB	PTSD	OCD	BPD	Total
Literature search									
Identified records, n	33,181	For all anxiety disorders: 19,535				36,108	11,235	11,827	111,886
Records after removal of duplicates, n	23,243	For all anxiety disorders: 13,328				14,369	7,752	5,867	64,559
Full texts assessed, n	3,987	For all anxiety disorders: 1,378				2,138	573	228	8,304
Studies and patients included									
Studies, n	159	48	52	48	22	69	22	21	441
Comparisons, n	196	71	74	61	32	87	26	22	569
Patients, N	14,908	3,559	4,053	3,773	1,189	2,986	1,011	1,525	33,881
Patients in therapy, N	8,362	2,236	2,593	2,162	711	2,325	585	795	19,769
Patients in control condition, N	6,546	1,323	1,460	1,611	478	1,538	426	730	14,112
Characteristics of included studies									
Clinical recruitment, n (%)	63 (38.9)	17 (35.4)	4 (7.7)	20 (41.7)	1 (4.2)	31 (44.9)	7 (31.8)	18 (85.7)	160 (36.3)
Age, years (mean±SD)	42.2±13.1	37.3±3.8	34.3±6.0	41.9±12.1	32.8±10.8	39.1±7.9	34.5±4.6	31.9±5.6	39.0±10.7
Proportion of women (mean±SD)	0.72±0.2	0.71±0.1	0.56±0.1	0.72±0.1	0.75±0.2	0.58±0.4	0.57±0.2	0.83±0.1	0.67±0.2
Type of control, n (%)									
Waitlist	68 (42.0)	36 (75.0)	44 (84.6)	34 (70.8)	23 (95.8)	54 (79.3)	16 (72.7)	0	270 (61.2)
Care-as-usual	89 (54.9)	6 (12.5)	4 (7.7)	11 (22.9)	1 (4.2)	13 (18.8)	4 (18.2)	21 (100.0)	149 (33.8)
Pill placebo	5 (3.1)	6 (12.5)	4 (7.7)	3 (6.2)	0	2 (3.9)	2 (9.1)	0	22 (5.0)
Country, n (%)									
North America	51 (31.5)	24 (50.0)	18 (34.6)	19 (39.6)	13 (54.2)	37 (53.6)	6 (27.3)	7 (33.3)	172 (39.0)
Europe	66 (40.7)	19 (39.6)	21 (40.4)	18 (37.5)	9 (37.5)	17 (24.6)	7 (31.8)	12 (57.1)	166 (37.6)
Other	45 (27.8)	5 (10.4)	13 (25.0)	11 (22.9)	2 (8.3)	15 (21.7)	9 (40.9)	2 (9.5)	103 (23.4)
Risk of bias (RoB)									
RoB tool	Version 1	Version 2	Version 2	Version 2	Version 2	Version 2	Version 2	Version 2	
Definition of low RoB	Low risk for four core items	Overall low RoB	Overall low RoB	Overall low RoB	Overall low RoB	Overall low RoB	Overall low RoB or some concerns	Overall low RoB or some concerns	
Low RoB, n (%)	64 (39.5)	3 (6.2)	4 (7.7)	8 (16.7)	3 (12.5)	6 (8.7)	3 (13.6)	2 (9.5)	93 (21.1)
Characteristics of interventions									
Format, n (%)									
Individual	80 (40.8)	39 (54.9)	29 (39.2)	34 (55.7)	23 (71.9)	70 (80.5)	12 (46.2)	8 (36.4)	295 (51.8)
Group	60 (30.6)	15 (21.2)	25 (33.8)	14 (23.0)	0	8 (9.2)	0	0	122 (21.4)
Guided self-help	34 (17.3)	12 (16.9)	17 (23.0)	13 (21.3)	1 (3.1)	5 (5.7)	4 (15.4)	0	86 (15.1)
Other/mixed	22 (11.2)	5 (7.0)	3 (4.1)	0	8 (25.0)	4 (4.6)	10 (38.5)	14 (63.4)	66 (11.6)
Sessions, n (mean±SD)	10.6±5.6	9.6±3.8	11.4±5.3	11.3±5.6	3.3±3.1	10.0±5.1	12.4±7.0	53.6±42.6	11.8±8.5

MDD – major depressive disorder, PAN – panic disorder, SAD – social anxiety disorder, GAD – generalized anxiety disorder, PHOB – specific phobia, PTSD – post-traumatic stress disorder, OCD – obsessive-compulsive disorder, BPD – borderline personality disorder

the baseline and post-test means and standard deviations of the continuous outcome measures, and the number of patients at post-test[24]. This method of estimating response rates has been tested in five meta-analyses of treatments of depression and anxiety[24,30], resulting in correlations between 0.94 and 0.97 between the estimated and true response rates.

Meta-analyses

We pooled the response rates using the *metaprop* function of the *meta* package in R (version 4.2.2), and ran all analyses in RStudio (2023.03.0+386). Binomial proportion data were first transformed to a logit scale, and then random-effects meta-analyses for the transformed data were conducted. Finally, the summary results were inverted to the raw binomial proportion scale, and the estimates and their 95% confidence intervals (CIs) were reported. Because we expected considerable heterogeneity, we employed a random-effects pooling model in all analyses (restricted maximum likelihood method).

After meta-analyzing the response rates, we pooled the RR of the intervention over the control condition across the included studies using the *metabin* function. The NNTs were calculated using the pooled RR and the response rate in the control group[31].

We conducted five sensitivity analyses: two with the less conservative estimates of the response rates (i.e., only including study completers, or considering all dropouts as responders), one in which we excluded outliers (studies in which the 95% CI of the rates did not overlap with the 95% CI of the pooled rates), one including only studies with low RoB, and one adjusting for publication bias. As an indicator of heterogeneity, we calculated the I^2 statistic and its 95% CI[32]. We examined potential publication bias using Egger's test of the intercept, and Duval and Tweedie trim-and-fill procedure.

We conducted a series of subgroup analyses, using mixed-effects methods, considering type of psychotherapy, treatment format, whether participants were recruited exclusively from clinical samples, type of control condition, and country where the study was carried out. Where possible, we avoided subgroups with less than five studies, clustering them into larger subgroups.

RESULTS

Selection, inclusion and characteristics of included studies

The searches across all disorders resulted in 111,886 records (64,559 after removal of duplicates), 8,304 full-text papers retrieved, and 441 studies included (see Table 1 for an overview, and supplementary information for the flow chart concerning each disorder). The number of included studies ranged from 159 (for MDD) to 21 (for BPD). Because several studies compared two or more interventions with one control group, the number of comparisons was larger (total: 569, ranging from 196 for MDD to 22 for BPD). The number of included patients was 33,881 (19,769 in treatment and 14,112 in control conditions), ranging from 1,011 in OCD to 14,908 in MDD dataset.

The proportion of patients exclusively recruited from clinical settings ranged from 4.2% for specific phobia to 85.7% for BPD, and was 36.3% across all disorders. The overall mean age was 39.0±10.7 years (range: 31.9±5.6 for BPD to 42.2±13.1 for MDD). The overall proportion of women was 67% (range: 56% for social anxiety disorder to 83% for BPD).

The type of control condition varied considerably across datasets. Waitlist was used in most trials in the four anxiety disorders (70.8% to 95.8%), PTSD (79.3%) and OCD (72.7%), but less frequently in MDD (42.0%) and not at all in BPD. Pill placebo was used in only a small proportion of studies (5.0% overall), while care-as-usual was the most used control condition in MDD (54.9%) and BPD (100%). Most trials were conducted in North America (39.0%) or Europe (37.6%).

Half of the interventions used an individual format (51.8%; range: 36.4% for BPD to 80.5% for PTSD). Group therapies were not used at all in some disorders (BPD, specific phobia and OCD) and ranged from 9.2% for PTSD to 33.8% for social anxiety disorder. Guided self-help was not used in BPD, and ranged from 3.1% for specific phobia to 23.0% for social anxiety disorder. The mean number of sessions across all disorders was 11.8±8.5 (range: 3.3 ±3.1 for specific phobia to 53.6±42.6 for BPD). The proportion of studies with low RoB ranged from 6.2% for panic disorder to 39.5% for MDD, but this should be considered with caution, because the definition of low RoB differed across datasets.

Response rates

Response rates in the psychotherapy conditions were 0.42 (95% CI: 0.39-0.45) for MDD; 0.38 (95% CI: 0.33-0.43) for PTSD; 0.38 (95% CI: 0.30-0.47) for OCD; 0.38 (95% CI: 0.33-0.43) for panic disorder; 0.36 (95% CI: 0.30-0.42) for GAD; 0.32 (95% CI: 0.29-0.37) for social anxiety disorder; 0.32 (95% CI: 0.23-0.42) for specific phobia; and 0.24 (95% CI: 0.15-0.36) for BPD (see Table 2 and Figure 1). Heterogeneity was moderate to high for all disorders (I^2 ranged from 65% for OCD to 82% for MDD and BPD).

When response rates were based on the least conservative assumption of all dropouts being responders, the outcomes were more positive (0.48 for MDD, 0.49 for PTSD, 0.44 for OCD, 0.42 for panic disorder, 0.40 for GAD, 0.33 for social anxiety disorder, 0.35 for specific phobia, and 0.35 for BPD). Heterogeneity remained moderate to large (I^2 range: 63 to 80%). Response rates based on completers only were 0.44 for MDD, 0.42 for PTSD, 0.40 for OCD, 0.40 for panic disorder, 0.37 for GAD, 0.34 for social anxiety disorder, 0.33 for specific phobia, and 0.26 for BPD (I^2 range: 64 to 80%).

Sensitivity analyses indicated that the number of studies with low RoB was very small across all disorders, except for MDD (see Table 3). For this condition, the response rate for psychotherapies in low RoB studies was somewhat smaller than in the main analyses, but not substantially (0.37; 95% CI: 0.33-0.42). Exclusion of outliers did not result in major changes of the response rates (all differences with respect to main analyses were smaller than 0.06). The same applied to adjustment for publication bias (all differences <0.08), except for BPD, which had a considerably larger response rate after adjustment (0.38 compared to 0.24).

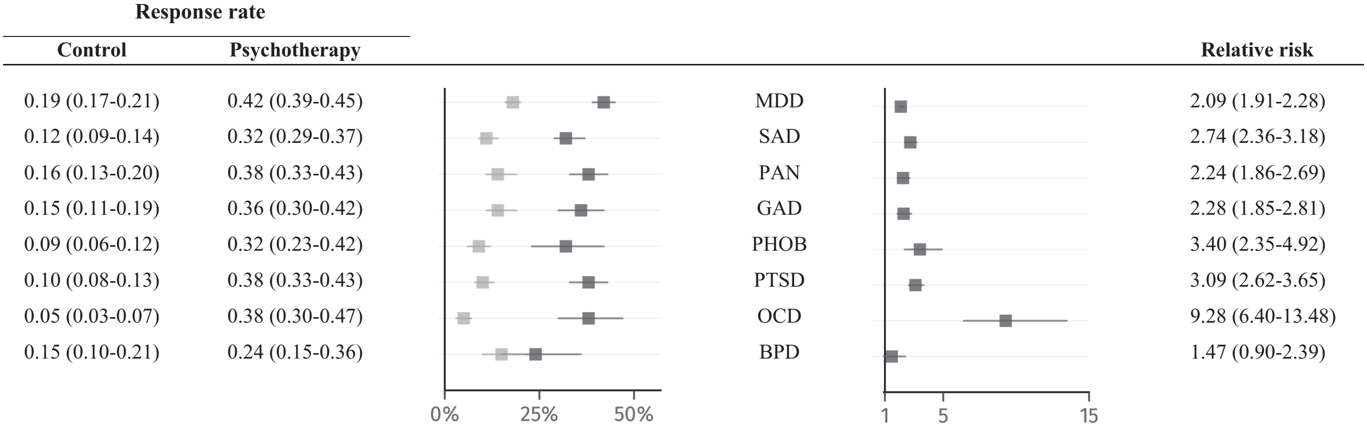
The overall response rates for the control conditions ranged from 0.05 for OCD to 0.19 for MDD, with heterogeneity (I^2) ranging from 0% for specific phobia and OCD to 75% for BPD. The rates were higher when all dropouts were considered responders (range: 0.09 to 0.23, I^2 range: 1% to 78%), and intermediate when only completers were included (range: 0.05 to 0.20; I^2 range: 0% to 72%) (see Table 2 and Figure 1).

The response rates for the control conditions in low RoB studies were comparable with those of the main analyses, except for BPD, which had a substantially larger rate in these studies (0.25 compared to 0.15). However, this was based on only three studies. The

Table 2 Response rates and relative outcomes across all psychotherapies and all disorders

	All psychotherapies					All control groups					Relative outcomes					
	n	Response rate	95% CI	I^2 (%)	95% CI	n	Response rate	95% CI	I^2 (%)	95% CI	RR	95% CI	I^2 (%)	95% CI	NNT	95% CI
Main outcomes																
MDD	196	0.42	0.39-0.45	82	79-84	162	0.19	0.17-0.21	72	67-76	2.09	1.91-2.28	40	29-50	4.8	4.1-5.8
SAD	74	0.32	0.29-0.37	66	56-73	52	0.12	0.09-0.14	45	23-60	2.74	2.36-3.18	0	0-28	4.8	3.8-6.1
PAN	71	0.38	0.33-0.43	77	71-82	48	0.16	0.13-0.20	61	46-71	2.24	1.86-2.69	47	31-60	5.0	3.7-7.3
GAD	61	0.36	0.30-0.42	74	67-80	48	0.15	0.11-0.19	71	61-78	2.28	1.85-2.81	24	0-45	5.2	3.7-7.8
PHOB	32	0.32	0.23-0.42	78	70-84	22	0.09	0.06-0.12	0	0-46	3.40	2.35-4.92	0	0-0.40	4.6	2.8-8.2
PTSD	87	0.38	0.33-0.43	74	68-79	69	0.10	0.08-0.13	44	25-58	3.09	2.62-3.65	0	0-26	4.8	3.8-6.2
OCD	26	0.38	0.30-0.47	65	47-77	22	0.05	0.03-0.07	0	0-46	9.28	6.40-13.48	0	0-43	2.4	1.6-3.7
BPD	22	0.24	0.15-0.36	82	73-87	21	0.15	0.10-0.21	75	61-83	1.47	0.90-2.39	27	0-57	14.2	-
All dropouts as responders																
MDD	196	0.48	0.45-0.51	80	77-83	162	0.23	0.20-0.26	78	75-81	1.99	1.81-2.18	51	43-59	4.4	3.7-5.4
SAD	74	0.33	0.29-0.37	66	56-73	52	0.12	0.09-0.14	45	23-60	2.74	2.36-3.18	0	0-28	4.8	3.8-6.1
PAN	71	0.42	0.37-0.48	80	75-84	48	0.18	0.15-0.23	70	60-78	2.19	1.87-2.57	49	33-62	4.7	3.5-6.4
GAD	61	0.40	0.34-0.46	76	69-81	48	0.17	0.13-0.22	69	59-77	2.18	1.80-2.65	57	43-68	5.0	3.6-7.4
PHOB	32	0.35	0.25-0.46	79	71-85	22	0.09	0.07-0.13	1	0-46	3.40	2.35-4.92	0	0-0.40	4.6	2.8-8.2
PTSD	87	0.49	0.44-0.54	71	65-77	69	0.17	0.14-0.20	55	41-66	2.75	2.36-3.20	22	0-44	3.4	2.7-4.3
OCD	26	0.44	0.36-0.52	63	44-76	22	0.10	0.07-0.15	15	0-49	4.10	2.79-6.02	0	0-43	3.2	2.0-5.6
BPD	22	0.35	0.25-0.47	78	67-85	21	0.23	0.17-0.31	71	55-81	1.48	1.09-2.02	23	0-54	8.2	3.8-43.5
Completers only																
MDD	196	0.44	0.41-0.48	80	77-82	162	0.20	0.18-0.22	72	67-76	2.12	1.93-2.32	42	31-51	4.5	3.8-5.4
SAD	74	0.34	0.30-0.38	68	59-75	52	0.12	0.09-0.15	47	27-62	2.73	2.34-3.17	0	0-28	4.8	3.8-6.2
PAN	71	0.40	0.35-0.45	78	72-82	48	0.16	0.13-0.21	64	51-73	2.27	1.89-2.72	48	31-60	4.9	3.6-7.0
GAD	61	0.37	0.31-0.44	75	68-80	48	0.15	0.12-0.20	67	55-75	2.29	1.86-2.82	46	26-60	5.2	3.7-7.8
PHOB	32	0.33	0.24-0.43	77	68-83	32	0.09	0.06-0.13	0	0-46	3.45	2.37-5.01	0	0-0.40	4.5	2.8-8.1
PTSD	87	0.42	0.38-0.47	68	60-74	69	0.11	0.09-0.14	40	20-56	3.48	2.97-4.08	0	0-26	3.7	3.0-4.6
OCD	26	0.40	0.32-0.49	64	45-76	22	0.05	0.03-0.08	0	0-46	9.28	6.42-13.40	0	0-43	2.4	1.6-3.7
BPD	22	0.26	0.17-0.39	79	70-86	21	0.16	0.11-0.23	72	57-82	1.50	0.95-2.37	24	0-55	12.5	-

RR – relative risk, NNT – number needed to treat, MDD – major depressive disorder, SAD – social anxiety disorder, PAN – panic disorder, GAD – generalized anxiety disorder, PHOB – specific phobia, PTSD – post-traumatic stress disorder, OCD – obsessive-compulsive disorder, BPD – borderline personality disorder



Response rate			
Control	Psychotherapy		Relative risk
0.19 (0.17-0.21)	0.42 (0.39-0.45)	MDD	2.09 (1.91-2.28)
0.12 (0.09-0.14)	0.32 (0.29-0.37)	SAD	2.74 (2.36-3.18)
0.16 (0.13-0.20)	0.38 (0.33-0.43)	PAN	2.24 (1.86-2.69)
0.15 (0.11-0.19)	0.36 (0.30-0.42)	GAD	2.28 (1.85-2.81)
0.09 (0.06-0.12)	0.32 (0.23-0.42)	PHOB	3.40 (2.35-4.92)
0.10 (0.08-0.13)	0.38 (0.33-0.43)	PTSD	3.09 (2.62-3.65)
0.05 (0.03-0.07)	0.38 (0.30-0.47)	OCD	9.28 (6.40-13.48)
0.15 (0.10-0.21)	0.24 (0.15-0.36)	BPD	1.47 (0.90-2.39)

Figure 1 Response rates and relative risks for response to psychotherapies (with 95% CIs in brackets). MDD – major depressive disorder, SAD – social anxiety disorder, PAN – panic disorder, GAD – generalized anxiety disorder, PHOB – specific phobia, PTSD – post-traumatic stress disorder, OCD – obsessive-compulsive disorder, BPD – borderline personality disorder. Grey boxes indicate control conditions and black boxes indicate psychotherapies.

exclusion of outliers did not result in major differences with the main analyses. Adjustment for publication bias resulted in rates that were higher than in the main analyses (see Table 3).

Subgroup analyses showed that type of psychotherapy was associated with differential response rates for MDD ($p<0.001$), panic disorder ($p=0.02$), specific phobia ($p=0.003$) and PTSD ($p<0.001$), but not for social anxiety disorder ($p=0.12$), GAD ($p=0.31$), OCD ($p=0.65$) and BPD ($p=0.59$) (see Table 4). Significantly different response rates were also found for treatment format in MDD, panic disorder, social anxiety disorder, GAD, specific phobia and PTSD, but not for OCD and BPD (see supplementary information). Recruitment from clinical samples was associated with a significantly smaller response rate in MDD and OCD, but not in the other disorders (see supplementary information). Significant differences between response rates in different countries were found for MDD, panic disorder, specific phobia, and BPD, but not for the other disorders (see supplementary information). Response rates differed significantly across type of control condition for MDD, panic disorder, and PTSD, but not for social anxiety disorder, GAD, and OCD. All trials in BPD had care-as-usual as the control condition, and all but one trial on specific phobia used waitlist (see supplementary information).

RRs and NNTs

Except for BPD, all RRs for psychotherapies were significant. They were 2.09 (95% CI: 1.91-2.28) for MDD; 3.09 (95% CI: 2.62-3.65) for PTSD; 9.28 (95% CI: 6.40-13.48) for OCD; 2.24 (95% CI: 1.86-2.69) for panic disorder; 2.28 (95% CI: 1.85-2.81) for GAD; 2.74 (95% CI: 2.36-3.18) for social anxiety disorder; 3.40 (95% CI: 2.35-4.92) for specific phobia; and 1.47 (95% CI: 0.90-2.39) for BPD (see Table 2 and Figure 1). Heterogeneity was low to moderate across all disorders (I^2 range: 0 to 47%).

The NNTs for the significant outcomes were 4.8 (95% CI: 4.1-5.8) for MDD; 4.8 (95% CI: 3.8-6.2) for PTSD; 2.4 (95% CI: 1.6-3.7) for OCD; 5.0 (95% CI: 3.7-7.3) for panic disorder; 5.2 (95% CI: 3.7-7.8) for GAD; 4.8 (95% CI: 3.8-6.1) for social anxiety disorder; and 4.6 (95% CI: 2.8-8.2) for specific phobia.

The RRs for the studies with low RoB and for the analyses in which the outliers were excluded were very comparable to those of the main analyses (all were significant except for BPD), except that the RR for BPD was also significant when outliers were excluded. In the analyses in which we adjusted for publication bias, all resulting RRs were smaller than in the main analyses, and the RR was no longer significant for panic disorder (see Table 3).

DISCUSSION

We conducted a large meta-analytic study to assess absolute and relative outcomes of psychotherapies across eight major mental disorders. The response rates in the treatment groups varied from 0.24 for BPD to 0.42 for MDD, while the rates for the other six disorders ranged from 0.32 to 0.39. Most sensitivity analyses broadly supported these findings, although the number of trials with low RoB was small, and in several samples significant indications for publication bias were identified. The pooled response rates across the three control conditions ranged from 0.05 for OCD to 0.19 for MDD. The relative outcomes we found in terms of RR were significant for all disorders, except BPD.

These results indicate that, although most psychotherapies lead to better outcomes compared to control conditions, response rates are modest. Most patients receiving psychotherapy across all disorders do not show at least 50% symptom reduction. This means that clinicians often have to try several interventions or move to pharmacological or combined therapies to treat patients more effectively. Unfortunately, very little research on such sequential treatments has been conducted.

There were significant differences between psychotherapies in terms of response rate in MDD, panic disorder, specific phobia and PTSD. Only one psychotherapy (i.e., dialectical behavior ther-

Table 3 Results of sensitivity analyses

	All psychotherapies					All control groups					Relative outcomes					
	n	Response rate	95% CI	I^2 (%)	95% CI	n	Response rate	95% CI	I^2 (%)	95% CI	RR	95% CI	I^2 (%)	95% CI	NNT	95% CI
Only low RoB																
MDD	71	0.37	0.33-0.42	86	83-88	64	0.19	0.16-0.22	75	68-80	1.82	1.61-2.06	25	0-45	6.4	5.0-8.6
SAD	5	0.76	0.32-0.95	89	78-95	4	0.14	0.04-0.38	73	23-90	3.50	1.23-9.90	10	0-81	2.9	0.8-31.1
PAN	4	0.22	0.14-0.32	74	27-91	3	0.12	0.02-0.47	88	68-96	1.89	0.50-7.05	39	0-79	9.4	-
GAD	9	0.44	0.28-0.60	82	67-90	8	0.17	0.13-0.23	29	0-68	2.30	1.64-3.25	13	0-54	4.5	2.6-9.2
PHOB	3	0.36	0.14-0.66	86	60-95	3	0.08	0.03-0.17	9	0-91	5.44	0.33-90.19	51	0-86	2.8	-
PTSD	7	0.43	0.31-0.55	66	24-85	6	0.09	0.06-0.15	0	0-75	3.62	1.71-7.63	18	0-62	4.2	1.7-15.6
OCD	3	0.44	0.21-0.71	62	0-89	3	0.09	0.03-0.24	0	0-90	5.24	0.07-406.51	0	0-90	2.6	-
BPD	4	0.49	0.20-0.78	90	77-96	3	0.25	0.07-0.59	87	64-96	1.45	0.72-2.91	69	10-89	8.9	-
Outliers excluded																
MDD	133	0.41	0.39-0.43	31	14-45	131	0.18	0.17-0.20	29	11-43	2.22	2.03-2.42	0	0-19	4.6	3.9-5.4
SAD	63	0.31	0.29-0.34	14	0-38	49	0.11	0.09-0.13	0	0-33	2.89	2.49-3.36	0	0-28	4.8	3.9-6.1
PAN	55	0.35	0.32-0.38	37	13-55	42	0.15	0.12-0.18	32	0-53	2.31	1.92-2.78	0	0-29	5.1	3.7-7.2
GAD	46	0.37	0.34-0.41	43	19-60	45	0.14	0.11-0.17	37	9-56	2.47	2.02-3.03	0	0-31	4.9	3.5-7.0
PHOB	26	0.24	0.19-0.30	39	2-62	22	0.09	0.06-0.12	0	0-46	3.40	2.35-4.92	0	0-0.40	4.6	2.8-8.2
PTSD	63	0.37	0.34-0.41	40	19-56	66	0.10	0.09-0.12	0	0-29	3.24	2.76-3.80	0	0-27	4.5	3.6-5.7
OCD	23	0.36	0.31-0.42	36	0-62	22	0.05	0.03-0.07	0	0-46	9.28	6.40-13.48	0	0-43	2.4	1.6-3.7
BPD	17	0.20	0.14-0.28	69	49-81	19	0.13	0.10-0.18	31	0-61	1.61	1.07-2.42	14	0-49	12.6	5.4-109.9
Adjusted for publication bias																
MDD	206	0.44	0.41-0.48	84	82-85	217	0.25	0.22-0.28	75	72-78	1.63	1.45-1.84	54	47-60	6.3	4.8-8.9
SAD	90	0.37	0.33-0.42	70	62-75	72	0.15	0.12-0.18	45	27-58	NC				NC	
PAN	71	0.38	0.33-0.44	77	71-82	66	0.23	0.18-0.29	64	53-72	1.29	0.96-1.73	55	43-64	15.0	-
GAD	68	0.40	0.33-0.46	76	70-81	68	0.24	0.18-0.31	73	66-79	1.66	1.26-2.20	31	9-47	6.3	3.5-16.0
PHOB	40	0.40	0.30-0.51	78	70-84		NC				2.94	1.97-4.38	0	0-36	5.7	3.3-11.5
PTSD	95	0.41	0.35-0.46	75	69-79	98	0.15	0.12-0.18	49	35-59	2.25	1.80-2.82	11	0-29	5.3	3.7-8.3
OCD	28	0.41	0.32-0.51	70	55-79	30	0.06	0.04-0.08	0	0-41	7.58	5.11-11.24	0	0-37	2.5	1.6-4.1
BPD	29	0.38	0.24-0.56	84	78-88	31	0.27	0.16-0.42	77	68-84	1.21	0.67-2.19	25	0-53	17.6	-

RoB – risk of bias, RR – relative risk, NNT – number needed to treat, MDD – major depressive disorder, SAD – social anxiety disorder, PAN – panic disorder, GAD – generalized anxiety disorder, PHOB – specific phobia, PTSD – post-traumatic stress disorder, OCD – obsessive-compulsive disorder, BPD – borderline personality disorder, NC – not calculable

Table 4 Response rates and relative outcomes for specific types of psychotherapies

		n	Response rate	95% CI	p	I^2 (%)	RR	95% CI	I^2 (%)	NNT	95% CI
MDD	CBT	110	0.44	0.39-0.48	<0.001	83	2.23	1.96-2.54	51	4.5	3.6-5.8
	Third wave	17	0.40	0.31-0.50		68	3.57	2.63-4.85	0	2.2	1.4-3.4
	BAT	9	0.53	0.42-0.65		74	2.13	1.35-3.36	24	4.9	2.4-15.9
	IPT	17	0.42	0.33-0.51		79	1.78	1.37-2.31	61	7.1	4.2-15.0
	PST	5	0.53	0.30-0.74		83	2.47	0.29-20.90	23	3.8	-
	SUP	6	0.36	0.17-0.60		88	1.38	0.94-2.04	0	14.6	-
	Controls	*157*	*0.19*	*0.17-0.21*		*73*					
PAN	CBT	42	0.41	0.35-0.47	0.02	80	2.42	1.90-3.09	57	5.0	3.4-7.9
	BT	10	0.35	0.25-0.47		55	4.55	2.00-10.31	0	2.0	0.8-7.1
	Relaxation	5	0.41	0.23-0.62		74	2.33	0.75-7.25	29	5.4	-
	Controls	*42*	*0.16*	*0.13-0.20*		*61*					
SAD	CBT	46	0.35	0.30-0.41	0.12	68	3.06	2.58-3.63	0	4.4	3.5-5.8
	Exposure	11	0.28	0.20-0.37		46	2.82	1.62-4.93	0	5.0	2.3-14.7
	Third wave	6	0.29	0.12-0.55		84	2.95	0.96-9.05	11	4.7	-
	Controls	*48*	*0.12*	*0.09-0.14*		*48*					
GAD	C(B)T	42	0.34	0.28-0.41	0.31	74	2.26	1.71-2.97	52	5.7	3.6-10.1
	Third wave	8	0.39	0.20-0.61		85	2.48	1.35-4.56	0	4.8	2.0-20.4
	Controls	*45*	*0.15*	*0.11-0.19*		*72*					
PHOB	Exposure	20	0.35	0.25-0.46	0.003	77	3.41	1.99-5.84	0	4.6	2.3-11.2
	CBT	7	0.39	0.15-0.71		87	4.61	2.14-9.93	0	3.1	1.2-9.7
	Controls	*22*	*0.09*	*0.06-0.12*		*0*					
OCD	CBT	13	0.38	0.31-0.45	0.65	50	8.68	5.36-14.07	0	2.6	1.5-4.6
	ERP	7	0.43	0.23-0.66		78	7.82	2.38-25.64	0	2.9	0.8-14.5
	Controls	*20*	*0.05*	*0.03-0.07*		*0*					
BPD	DBT	7	0.24	0.08-0.55	0.59	86	1.56	0.98-2.46	0	11.9	-
	Controls	*21*	*0.15*	*0.10-0.21*		*75*					
PTSD	TF-CBT	22	0.35	0.28-0.44	<0.001	69	2.57	2.12-3.12	0	6.4	4.7-8.9
	TF-exposure	21	0.36	0.29-0.44		62	3.90	2.91-5.22	0	3.4	2.4-5.2
	EMDR	9	0.34	0.19-0.53		71	4.19	1.90-9.21	21	3.1	1.2-11.1
	NTF-CBT	11	0.35	0.20-0.54		80	2.58	1.47-4.51	0	6.3	2.8-21.3
	TF-CT	8	0.52	0.33-0.70		83	5.32	3.11-9.08	0	2.3	1.2-4.7
	Controls	*67*	*0.10*	*0.08-0.13*		*36*					

Comparisons with pill placebo are not included, because response rates in this group differed considerably from those in the other control groups. RR – relative risk, NNT – number needed to treat, MDD – major depressive disorder, PAN – panic disorder, SAD – social anxiety disorder, GAD – generalized anxiety disorder, PHOB – specific phobia, PTSD – post-traumatic stress disorder, OCD – obsessive-compulsive disorder, BPD – borderline personality disorder, CBT – cognitive behavior therapy, BAT – behavioral activation therapy, IPT – interpersonal psychotherapy, PST – problem-solving therapy, SUP – supportive therapy, BT – behavior therapy, ERP – exposure and response prevention, DBT – dialectical behavior therapy, TF– trauma focused, EMDR – eye movement desensitization and reprocessing, NTF – non-trauma focused.

apy) was tested in BPD, and its response rate was not significantly higher than the care-as-usual control condition, typically consisting of intensive treatment, which suggests that specific psychotherapies for BPD may have limited additional benefit. This implication, however, should be considered with caution, because some meta-analyses exclusively dealing with BPD are broader and may give a better estimate of the effects of psychotherapies[16,17].

There are some limitations of this study that need to be considered. We expected and found high levels of heterogeneity, although most response rates were relatively robust in a series of sensitivity analyses. We found that the number of trials with low RoB was limited, meaning that the findings should be taken with caution. The included meta-analytic datasets also used different ways of defining low RoB, so that we cannot compare RoB across datasets. The response rates were not directly reported in the studies but were estimated. Although the method we adopted has been well validated, these are still estimates and this may have affected the pooled rates.

We could only include trials that reported enough data to calculate the response rates, and this may have resulted in selection bias. We only examined response rates after treatment and did not take the time to follow-up into account, which may have introduced additional heterogeneity. Furthermore, we chose a 50% symptom reduction as the main outcome, which is the standard in depression, but may not be the best choice for other disorders, for which no clear standards exist[25,26]. Finally, we did not examine differences across studies in patient characteristics that can affect outcomes (e.g., gender, and veteran status in PTSD)[33].

This is the first meta-analysis of trials examining the effects of psychotherapies for eight different mental disorders, established with a diagnostic interview. It is also the first to report the absolute measure of response rate next to relative outcomes, using the same definition of response (number of patients with at least 50% symptom reduction between baseline and post-test, divided by the total number of patients) across the mental disorders. The results of this study can contribute to improved clinical decision-making and technology-supported tools[34].

We conclude that most psychotherapies for the eight mental disorders are effective compared to control conditions, but that the response rates are modest, ranging from 0.24 for BPD to 0.42 for MDD. More effective interventions, as well as therapies for those not responding to a first-line treatment, are clearly needed.

ACKNOWLEDGEMENT

Supplementary information on this study is available at https://osf.io/2htsv.

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DOI:10.1002/wps.21203

Real-world effectiveness of antidepressants, antipsychotics and their combinations in the maintenance treatment of psychotic depression. Evidence from within-subject analyses of two nationwide cohorts

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Psychotic depression (PD) is a severe mental disorder leading to functional disability and high risk of suicide, but very little is known about the comparative effectiveness of medications used in its maintenance treatment. The objective of this study was to investigate the comparative effectiveness of specific antipsychotics and antidepressants, and their combinations, on the risk of psychiatric hospitalization among persons with PD in routine care. Persons aged 16-65 years with a first-time diagnosis of PD were identified from Finnish (years 2000-2018) and Swedish (years 2006-2021) nationwide registers of inpatient care, specialized outpatient care, sickness absence, and disability pension. The main exposures were specific antipsychotics and antidepressants, and the main outcome measure was psychiatric hospitalization as a marker of severe relapse. The risk of hospitalization associated with periods of use vs. non-use of medications (expressed as adjusted hazard ratio, aHR) was assessed by a within-individual design, using each individual as his/her own control, and analyzed with stratified Cox models. The two national cohorts were first analyzed separately, and then combined using a fixed-effect meta-analysis. The Finnish cohort included 19,330 persons (mean age: 39.8±14.7 years; 57.9% women) and the Swedish cohort 13,684 persons (mean age: 41.3±14.0 years; 53.5% women). Individual antidepressants associated with a decreased risk of relapse vs. non-use of antidepressants were bupropion (aHR=0.73, 95% CI: 0.63-0.85), vortioxetine (aHR=0.78, 95% CI: 0.63-0.96) and venlafaxine (aHR=0.92, 95% CI: 0.86-0.98). Any long-acting injectable antipsychotic (LAI) (aHR=0.60, 95% CI: 0.45-0.80) and clozapine (aHR=0.72, 95% CI: 0.57-0.91) were associated with a decreased risk of relapse vs. non-use of antipsychotics. Among monotherapies, only vortioxetine (aHR=0.67, 95% CI: 0.47-0.95) and bupropion (aHR=0.71, 95% CI: 0.56-0.89) were associated with a significantly decreased risk of relapse vs. non-use of both antidepressants and antipsychotics. In an exploratory analysis of antidepressant-antipsychotic combinations, a decreased relapse risk was found for amitriptyline-olanzapine (aHR=0.45, 95% CI: 0.28-0.71), sertraline-quetiapine (aHR=0.79, 95% CI: 0.67-0.93) and venlafaxine-quetiapine (aHR=0.82, 95% CI: 0.73-0.91) vs. non-use of antidepressants and antipsychotics. Benzodiazepines and related drugs (aHR=1.29, 95% CI: 1.24-1.34) and mirtazapine (aHR=1.17, 95% CI: 1.07-1.29) were associated with an increased risk of relapse. These data indicate that, in the maintenance treatment of PD, bupropion, vortioxetine, venlafaxine, any LAI, clozapine, and only few specific antidepressant-antipsychotic combinations are associated with a decreased risk of relapse. These findings challenge the current recommendation by treatment guidelines to combine an antipsychotic with an antidepressant (without further specification) as standard treatment in PD.

Key words: Psychotic depression, antidepressants, antipsychotics, antidepressant-antipsychotic combinations, maintenance treatment, bupropion, vortioxetine, LAIs, clozapine

(World Psychiatry 2024;23:276–284)

Major depression with psychotic features (such as delusions or hallucinations), also known as psychotic depression (PD), is a severe mental disorder with an estimated point prevalence of 0.4%[1]. People aged 18-27 and 58-65 years are over-represented in PD vs. non-psychotic severe depression[2], and the disorder is also relatively common among people aged >65 years[1]. PD is considered the most severe form of major depressive disorder, due its high risk of relapse and recurrence, as well as mortality, especially due to suicide and fatal accidents[1-3].

The current prevalent opinion, reflected in treatment guidelines, is that PD should be treated with a combination of an antidepressant and an antipsychotic[4], or with electroconvulsive therapy[5]. A recent Cochrane review[6] concluded that the antidepressant-antipsychotic combination may be more effective in the acute treatment of PD than either antidepressant or antipsychotic monotherapy. However, the two comparisons were based, respectively, on only five and four randomized controlled trials (RCTs), and the certainty of evidence was rated as low to very low. The review found no evidence of a superiority of an antidepressant or an antipsychotic over placebo, but both comparisons were based on only one study, and the certainty of evidence was rated as very low. Thus, the recommendation to use the antidepressant-antipsychotic combination has a limited research support. Indeed, there are reports that, in ordinary clinical practice, antidepressant monotherapy is the most common treatment for acute PD[7,8].

Most patients recover from the acute episode of PD, and the main burden of this condition comes from its relapsing nature, resulting into chronic suffering and working disability[9]. Very little is known about the effectiveness of maintenance treatments for PD. The only RCT conducted thus far concluded that olanzapine plus sertraline was more effective in relapse prevention than placebo plus sertraline[10]. Additionally, only one open-label 15-week extension[11] of a 7-week acute randomized trial[12] assessed the maintenance efficacy of an antidepressant-antipsychotic combination vs. antidepressant monotherapy in initial responders, finding no group differences.

Data on the comparative effectiveness of different pharmacotherapies in PD are sparse for acute episodes and lacking for relapse prevention. Indeed, even if just the five most widely used antipsychotics and antidepressants were studied as monotherapy or as antipsychotic-antidepressant pairs, there would be 35 different treatment options to test. Thousands of patients would be required to achieve a sufficient statistical power. While it would be unfeasible to recruit such a large patient sample in an RCT, assessing the relevant outcomes in large samples is possible in observational studies using nationwide cohorts. However, we are not aware of any observational investigation on the real-world effectiveness of antidepressants and antipsychotics or their combinations in the relapse prevention of PD.

The aim of this study was to investigate the comparative effectiveness of specific antipsychotics and antidepressants, and their combinations, on the risk of psychiatric hospitalization – regarded as a proxy for relapse, as in previous studies with real-world data[13-15] – among persons with first-episode PD.

METHODS

Patient cohorts

The study and the analyses were conducted using data from two countries, Finland and Sweden, which were then meta-analyzed together.

The Finnish cohort comprised the persons with first-episode PD diagnosed in the period 2000-2018, at the age of 16-65 years, without a previous diagnosis of schizophrenia or bipolar disorder (since 1987), identified from Finnish nationwide registers. PD was defined on the basis of ICD-10 codes F32.3 and F33.3. The registers utilized for cohort identification were those of inpatient and specialized outpatient care (Care Register for Health Care), sickness absence (Social Insurance Institution, SII), and disability pension (SII and Centre for Pensions).

Data for the cohort were linked to other nationwide registries, including the Prescription Register, which contains drug dispensing records of all reimbursed drugs. The data linkage was conducted by the register maintainers utilizing a unique personal identification number, which is assigned to all residents of the country at birth or immigration. The data were pseudonymized and the participants were not contacted in any way. The study was exempt from ethics committee approval under the Finnish law. The research project was reviewed and approved by the institutions responsible for maintaining the registers: the Finnish National Institute for Health and Welfare (635/5.05.00/2019), the SII of Finland (31/522/2019), Finnish Centre for Pensions (19023) and Statistics Finland (TK-53-56919).

The Swedish cohort included the persons with first-episode PD (ICD-10 codes F32.3 and F33.3) diagnosed in the period 2006-2021, at the age of 16-65 years, without a previous diagnosis of schizophrenia or bipolar disorder (since 1969). They were identified from the National Patient Register (including inpatient and specialized outpatient care) and the MiDAS register (including sickness absence and disability pension). Cohort entry was restricted to year 2006 as the Prescribed Drug Register was opened in July 2005. The project was approved by the Regional Ethical Review Board of the Karolinska Institutet (2007/762-31 and 2021-06441-02).

Procedures

For both cohorts, the follow-up started at first diagnosis (discharge date from hospital for those who were in inpatient care at the time of their first diagnosis). It ended at death, diagnosis of schizophrenia or bipolar disorder, or end of data linkage (December 31, 2018 for the Finnish cohort, and December 31, 2021 for the Swedish cohort), whichever occurred first.

The main exposures were individual antidepressants (Anatomical Therapeutic Chemical, ATC code N06A) and antipsychotics (N05A, excluding lithium). All long-acting injectable antipsychotics (LAIs) were grouped together as "any LAI". Concomitant use of multiple antidepressants was coded as "AD polytherapy", and the same was done for antipsychotics. We further categorized antipsychotics as weak dopamine D2 blockers (aripiprazole, clozapine, olanzapine and quetiapine, including both oral and LAI forms) and strong D2 blockers (the others)[16].

Drug use periods (i.e., when drug use started and ended) were constructed with a validated mathematical modeling method called PRE2DUP[17]. This method calculates drug use periods using dispensing dates, dispensed amounts, and drug package-specific parameters, which define clinically relevant upper and lower limits for daily dosage. The method takes into account individual purchasing regularity, stockpiling, and hospital care periods when drugs are provided by the caring unit and thus are not recorded in the register.

The main outcome measure was psychiatric hospitalization (relapse), i.e. hospitalization due to any mental disorder (ICD-10 F codes), intentional self-harm (X60-X84) or injury/poisoning of undetermined intent (Y10-Y34). The secondary outcome measure was hospitalization due to affective disorders (ICD-10 codes F30-F39). Outcomes were treated as recurrent events, meaning that they could occur multiple times during the follow-up for the same person.

Statistical analyses

We utilized a within-individual design in which each person acts as his/her own control to minimize selection bias, as all time-invariant factors (such as genetics, sex, personal history before cohort inclusion) are automatically controlled for. Time is reset to zero after each outcome event. The stratified Cox models were adjusted for time-varying factors, which were other medication use, time since cohort entry, and temporal order of treatments.

Antidepressant analyses were adjusted for concomitant antipsychotic use and vice versa. In secondary analyses, other psychotropic drugs – i.e., mood stabilizers (carbamazepine, valproic acid, lamotrigine and lithium) and benzodiazepines or related drugs (i.e., Z-drugs) – were also analyzed as exposures.

The analyses were conducted separately in the Finnish and Swedish cohorts. The results were then combined using a fixed-effect meta-analysis. In drug-specific analyses of antidepressants, the reference category was non-use of antidepressants; in drug-specific analyses of antipsychotics, it was non-use of antipsychotics. Additional analyses were conducted as head-to-head comparisons to the most commonly used antidepressant (i.e., mirtazapine) or antipsychotic (i.e., quetiapine).

For analyses of "antidepressant only" (without concomitant antipsychotic, termed antidepressant "monotherapy") and "antipsychotic only" ("antipsychotic monotherapy"), as well as for two-drug antidepressant-antipsychotic combinations, the reference category was non-use of both antidepressants and antipsychotics. In these analyses, all one-drug categories (e.g., citalopram only, without any concomitant antipsychotics) were also re-analyzed, as the reference category was different from the drug-specific analyses.

Sensitivity analyses were conducted by censoring the first 30 days from all exposures, to account for protopathic bias (i.e., drugs are often started when the symptoms are worsening) and because the full therapeutic effect takes time to occur. Further, sensitivity analyses excluding persons who received a diagnosis of schizophrenia or bipolar disorder during the follow-up were conducted, to ensure that they did not drive the results. Lastly, sensitivity analyses in which low-dose (<18 mg/day) mirtazapine use (which is common for insomnia) was omitted from analyses concerning this drug were conducted in the Finnish dataset, where dose modelling was available.

Data management and within-individual analyses were run with SAS 9.4, and meta-analysis with RStudio, *metafor* package

Table 1 Risk of psychiatric hospitalization associated with specific antidepressants and antipsychotics in Finnish and Swedish cohorts

	Finnish cohort				**Swedish cohort**			
	Events	**Users**	**PYs**	**aHR (95% CI)**	**Events**	**Users**	**PYs**	**aHR (95% CI)**
Antidepressants								
Bupropion	184	1,208	1,077	0.74 (0.59-0.93)	213	1,030	879	0.73 (0.60-0.88)
Vortioxetine	93	638	320	0.77 (0.57-1.06)	111	472	433	0.78 (0.59-1.03)
Sertraline	920	2,622	4,470	0.86 (0.77-0.97)	1,310	3,594	5,593	1.01 (0.91-1.13)
Venlafaxine	3,069	5,454	11,970	0.91 (0.84-0.98)	1,337	2,704	5,145	0.94 (0.84-1.05)
Duloxetine	584	1,545	2,233	0.97 (0.84-1.12)	695	1,603	2,389	1.07 (0.94-1.22)
Fluoxetine	632	1,679	2,232	0.99 (0.86-1.14)	682	1,346	2,001	1.06 (0.92-1.21)
Paroxetine	444	1,022	1,786	1.00 (0.84-1.18)	206	419	699	1.09 (0.85-1.40)
Citalopram	1,254	3,434	6,325	1.00 (0.90-1.11)	408	1,535	2,158	1.15 (0.96-1.38)
Escitalopram	1,410	4,163	5,718	1.01 (0.91-1.11)	879	2,418	3,412	1.04 (0.92-1.17)
Antidepressant polytherapy	5,469	9,595	13,408	1.01 (0.94-1.08)	3,794	7,272	10,036	1.02 (0.94-1.10)
Amitriptyline	221	811	961	1.07 (0.87-1.33)	172	742	724	0.90 (0.70-1.16)
Mirtazapine	1,914	5,414	6,544	1.11 (1.02-1.21)	1,203	3,760	3,840	1.17 (1.06-1.30)
Non-use of antidepressants	6,921	15,604	60,159	Reference	5,663	11,219	40,512	Reference
Antipsychotics								
Any LAI	42	108	135	0.43 (0.28-0.67)	51	88	71	0.77 (0.52-1.13)
Clozapine	109	111	201	0.76 (0.58-0.99)	40	39	108	0.61 (0.38-0.98)
Levomepromazine	460	808	1,071	0.93 (0.81-1.07)	293	626	516	1.06 (0.89-1.26)
Quetiapine	4,784	8,145	16,686	0.93 (0.88-1.00)	1,492	2,945	3,842	1.02 (0.93-1.11)
Olanzapine	2,079	3,775	5,956	0.99 (0.91-1.08)	1,963	4,751	5,263	0.98 (0.90-1.07)
Antipsychotic polytherapy	3,473	5,390	5,225	1.04 (0.97-1.12)	1,827	2,933	2,231	1.11 (1.02-1.21)
Perphenazine	433	1,160	1,501	1.05 (0.90-1.24)	46	106	105	0.81 (0.49-1.32)
Aripiprazole	484	1,088	1,160	1.07 (0.93-1.24)	553	1,511	1,679	1.01 (0.88-1.15)
Risperidone	1,673	3,800	5,677	1.07 (0.97-1.17)	671	1,888	2,092	1.02 (0.89-1.16)
Haloperidol	77	203	139	1.13 (0.81-1.59)	128	399	311	0.71 (0.54-0.92)
Flupentixol	71	179	142	1.63 (1.12-2.37)	111	308	342	1.07 (0.79-1.46)
Non-use of antipsychotics	9,792	17,206	80,798	Reference	10,138	13,034	63,023	Reference

PYs – person-years, aHR – adjusted hazard ratio, LAI – long-acting injectable antipsychotic

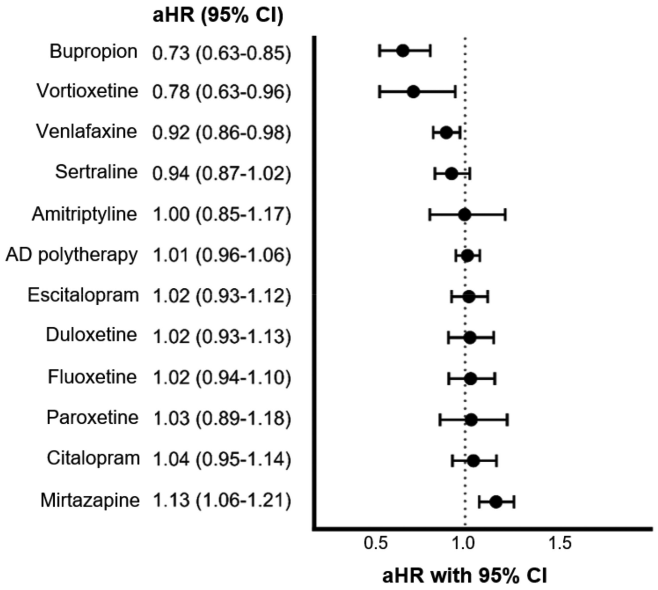

Figure 1 Risk of psychiatric hospitalization associated with specific antidepressants compared with non-use of antidepressants in fixed-effect meta-analysis. aHR – adjusted hazard ratio, AD – antidepressant.

(version 3.0-2). The results are reported as adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs).

RESULTS

The Finnish cohort included 19,330 individuals. Their mean age was 39.8±14.7 years, and 57.9% of them were women. The Swedish cohort included 13,684 individuals (mean age 41.3±14.0 years; 53.5% women).

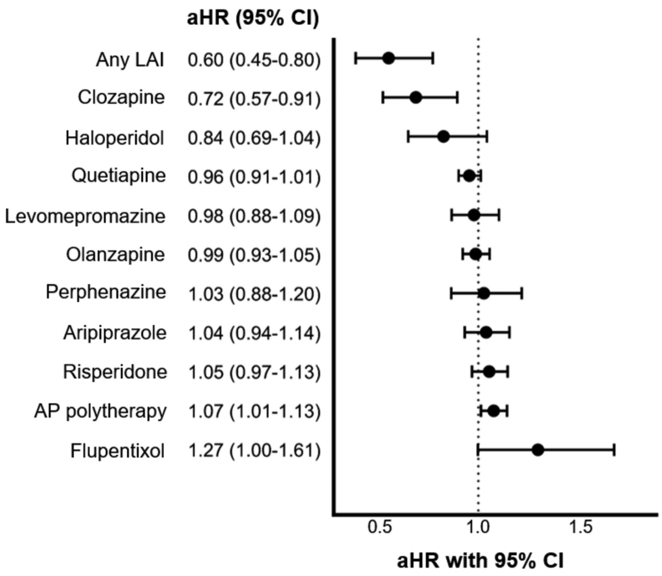

Figure 2 Risk of psychiatric hospitalization associated with specific antipsychotics compared with non-use of antipsychotics in fixed-effect meta-analysis. aHR – adjusted hazard ratio, AP – antipsychotic, LAI – long-acting injectable antipsychotic.

Of the Finnish cohort, 39.0% (N=8,106) experienced relapse during the follow-up (median follow-up time: 5.1 years; interquartile range, IQR: 1.4-10.6). The corresponding figure in the Swedish cohort was 47.6% (N=6,511) and the median follow-up time was 5.1 years (IQR: 1.8-9.8).

During the follow-up, antidepressants were used by 87.9% of persons (N=17,000) and antipsychotics by 74.4% of persons (N=14,378) in the Finnish cohort. The corresponding figures in the Swedish cohort were 88.9% (N=12,166) and 66.5% (N=9,097). In the Finnish sample, venlafaxine was the most commonly used antidepressant (28.2%, N=5,454), followed by mirtazapine (28.0%, N=5,414) and escitalopram (21.5%, N=4,163). In the Swedish sample, the most commonly used antidepressant was mirtazapine

Table 2 Risk of psychiatric hospitalization associated with specific antidepressants and antipsychotics compared to the most commonly used antidepressant (mirtazapine) or antipsychotic (quetiapine) in Finnish and Swedish cohorts and in fixed-effect meta-analysis

	Finnish cohort aHR (95% CI)	Swedish cohort aHR (95% CI)	Fixed-effect meta-analysis aHR (95% CI)
Antidepressants (ref. mirtazapine)			
Bupropion	0.67 (0.53-0.85)	0.62 (0.50-0.77)	0.64 (0.55-0.75)
Vortioxetine	0.70 (0.51-0.96)	0.67 (0.50-0.89)	0.68 (0.55-0.84)
Venlafaxine	0.82 (0.74-0.90)	0.80 (0.70-0.92)	0.81 (0.75-0.88)
Sertraline	0.78 (0.68-0.89)	0.87 (0.76-0.99)	0.82 (0.75-0.90)
Amitriptyline	0.97 (0.78-1.21)	0.77 (0.60-1.00)	0.88 (0.74-1.04)
Duloxetine	0.87 (0.75-1.02)	0.91 (0.79-1.06)	0.89 (0.80-0.99)
Antidepressant polytherapy	0.91 (0.83-0.99)	0.87 (0.79-0.96)	0.89 (0.84-0.95)
Fluoxetine	0.89 (0.77-1.04)	0.90 (0.77-1.06)	0.90 (0.81-1.00)
Escitalopram	0.91 (0.81-1.02)	0.88 (0.77-1.02)	0.90 (0.82-0.98)
Paroxetine	0.90 (0.75-1.08)	0.93 (0.72-1.21)	0.91 (0.79-1.06)
Citalopram	0.90 (0.80-1.02)	0.99 (0.81-1.20)	0.92 (0.83-1.02)
Antipsychotics (ref. quetiapine)			
Any LAI	0.47 (0.30-0.72)	0.76 (0.51-1.11)	0.61 (0.46-0.81)
Clozapine	0.81 (0.62-1.06)	0.60 (0.37-0.97)	0.76 (0.60-0.95)
Haloperidol	1.21 (0.87-1.70)	0.69 (0.53-0.91)	0.86 (0.70-1.07)
Levomepromazine	1.00 (0.86-1.15)	1.04 (0.87-1.25)	1.01 (0.91-1.14)
Olanzapine	1.06 (0.97-1.16)	0.97 (0.87-1.08)	1.03 (0.96-1.10)
Aripiprazole	1.15 (0.99-1.33)	0.99 (0.85-1.15)	1.07 (0.96-1.18)
Perphenazine	1.13 (0.96-1.33)	0.79 (0.48-1.30)	1.09 (0.93-1.27)
Risperidone	1.14 (1.04-1.26)	1.00 (0.86-1.16)	1.10 (1.01-1.19)
Antipsychotic polytherapy	1.12 (1.04-1.20)	1.10 (0.99-1.21)	1.11 (1.05-1.17)
Flupentixol	1.74 (1.20-2.55)	1.05 (0.77-1.45)	1.30 (1.02-1.65)

aHR – adjusted hazard ratio, LAI – long-acting injectable antipsychotic

(27.5%, N=3,760), followed by sertraline (26.3%, N=3,594) and venlafaxine (19.8%, N=2,704). Quetiapine (42.1%, N=8,145) was the most commonly used antipsychotic in the Finnish cohort, followed by risperidone (19.6%, N=3,800), whereas olanzapine was the most frequently used antipsychotic in the Swedish cohort (34.7%, N= 4,751) followed by quetiapine (21.5%, N=2,945) (see Table 1).

Compared with non-use of antidepressants, bupropion (aHR= 0.73, 95% CI: 0.63-0.85), vortioxetine (aHR=0.78, 95% CI: 0.63-0.96) and venlafaxine (aHR=0.92, 95% CI: 0.86-0.98) were associated with a decreased risk of relapse (see Figure 1). This was also true for any LAI (aHR=0.60, 95% CI: 0.45-0.80) and clozapine (aHR=0.72, 95% CI: 0.57-0.91) compared with non-use of antipsychotics (see Figure 2).

When compared in head-to-head within-individual analysis to the most commonly used antidepressant across the two cohorts (mirtazapine), bupropion (aHR= 0.64, 95% CI: 0.55-0.75), vortioxetine (aHR=0.68, 95% CI: 0.55-0.84), venlafaxine (aHR=0.81, 95% CI: 0.75-0.88), sertraline (aHR=0.82, 95% CI: 0.75-0.90), duloxetine (aHR=0.89, 95% CI: 0.80-0.99), antidepressant polytherapy (aHR= 0.89, 95% CI: 0.84-0.95) and escitalopram (aHR=0.90, 95% CI: 0.82-

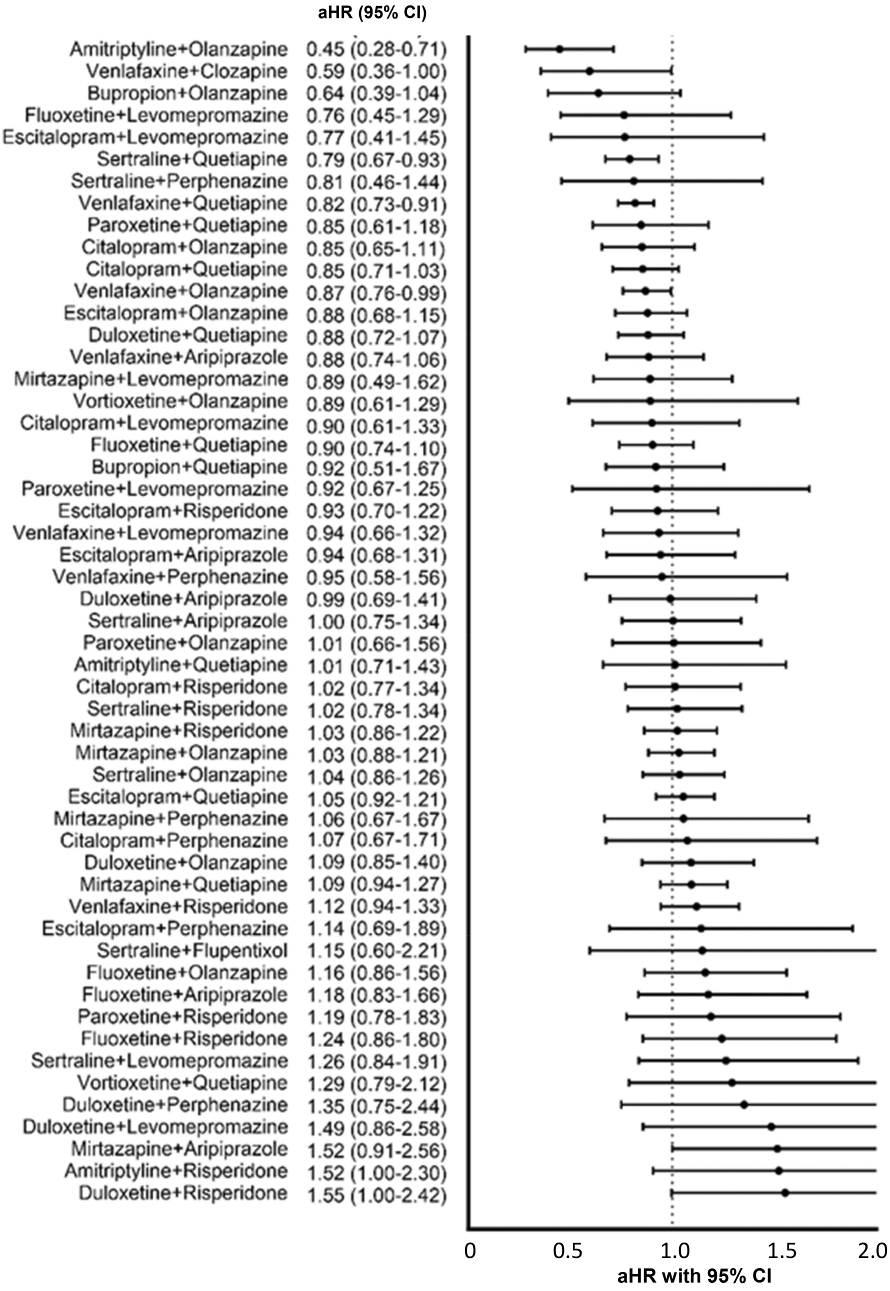

Figure 3 Risk of psychiatric hospitalization associated with two-drug combinations of the ten most common antipsychotics and the eleven most common antidepressants compared with non-use of both antipsychotics and antidepressants. aHR – adjusted hazard ratio.

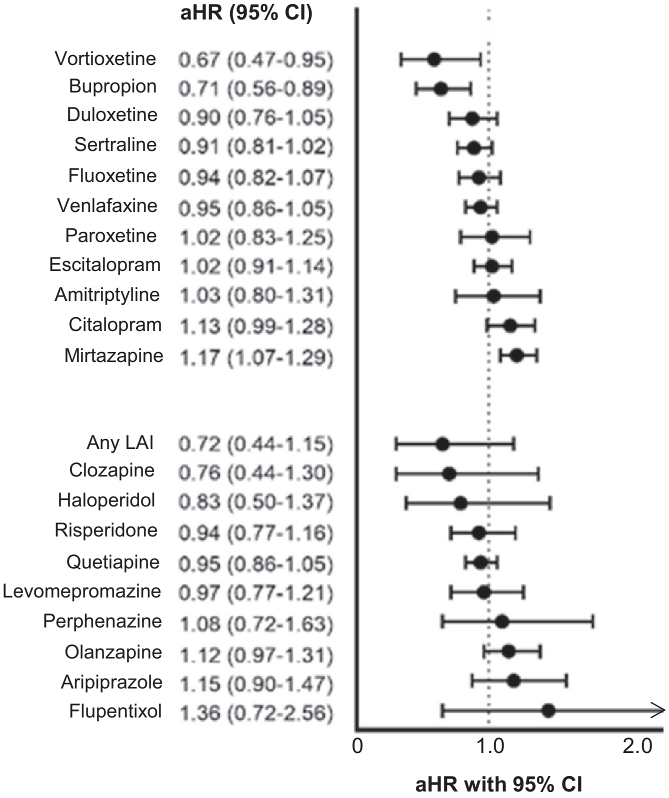

Figure 4 Risk of psychiatric hospitalization associated with use of the ten most common antipsychotics and the eleven most common antidepressants in monotherapy, compared with non-use of both antipsychotics and antidepressants. aHR – adjusted hazard ratio, LAI – long-acting injectable antipsychotic.

0.98), were associated with decreased risk of relapse (see Table 2).

When compared in head-to-head within-individual analysis to the most common antipsychotic across the two cohorts (quetiapine), any LAI (aHR=0.61, 95% CI: 0.46-0.81) and clozapine (aHR= 0.76, 95% CI: 0.60-0.95) were associated with decreased risk of relapse (see Table 2). Among antipsychotics, flupentixol (aHR=1.30, 95% CI:1.02-1.65) and risperidone (aHR=1.10, 95% CI: 1.01-1.19) were associated with an increased risk of relapse compared to quetiapine.

In sensitivity analyses in which the first 30 days were removed from all use periods, a similar rank order was observed, with somewhat reduced statistical power. Between-individual analyses also showed a similar rank order, with any LAI and bupropion having the lowest aHRs. The results were also similar in random-effects meta-analysis, except that they were no longer significant for any LAI. When excluding persons whose diagnosis transitioned to schizophrenia or bipolar disorder during the follow-up, the results did not change (see supplementary information). When excluding low-dose (<18 mg/day) mirtazapine use from the analysis of the Finnish cohort, the results for this drug did not change (aHR=1.19, 95% CI: 1.09-1.31).

When the two-drug combinations of the ten most commonly used antipsychotics and the eleven most commonly used antidepressants were considered, amitriptyline-olanzapine (aHR=0.45, 95% CI: 0.28-0.71), sertraline-quetiapine (aHR=0.79, 95% CI: 0.67-0.93) and venlafaxine-quetiapine (aHR=0.82, 95% CI:0.73-0.91) were associated with a decreased risk of relapse compared to non-use of both antipsychotics and antidepressants (see Figure 3).

Among antidepressants used as monotherapy, only vortioxetine (aHR=0.67, 95% CI: 0.47-0.95) and bupropion (aHR=0.71, 95% CI: 0.56-0.89) were associated with decreased risk of relapse when compared to non-use of both antidepressants and antipsychotics. Among antipsychotics used as monotherapy, none was associated with decreased risk of relapse as compared to non-use of both antidepressants and antipsychotics (see Figure 4).

The combination between an antidepressant and a weak D2-blocking antipsychotic was associated with a decreased risk of relapse (aHR=0.92, 95% CI: 0.87-0.98) compared with non-use of both antipsychotics and antidepressants, whereas the combination between an antidepressant and a strong D2-blocking antipsychotic was not (aHR=1.03, 95% CI: 0.95-1.11). The latter was also true for use of a strong D2-blocking antipsychotic without antidepressant (aHR=0.98, 95% CI: 0.86-1.13), of a weak D2-blocking antipsychotic without antidepressant (aHR=0.99, 95% CI: 0.91-1.08), or of any antidepressant without antipsychotic (aHR=1.00, 95% CI: 0.94-1.05).

Any antidepressant use was not associated with a decreased risk of relapse compared with antidepressant non-use (aHR=1.01, 95% CI: 0.97-1.05). Any antipsychotic use was not associated with a decreased risk of relapse compared to antipsychotic non-use (aHR=0.99, 95% CI: 0.96-1.03). Any antidepressant-antipsychotic

Table 3 Risk of psychiatric hospitalization associated with benzodiazepines and related drugs (compared with non-use of these drugs) and specific mood stabilizers (compared with non-use of mood stabilizers) in Finnish and Swedish cohorts and in fixed-effect meta-analysis

	Finnish cohort				Swedish cohort				Fixed-effect meta-analysis aHR (95% CI)
	Events	Users	PYs	aHR (95% CI)	Events	Users	PYs	aHR (95% CI)	
Benzodiazepines and related drugs	11,527	11,120	29,400	1.23 (1.17-1.29)	7,943	8,940	17,279	1.39 (1.31-1.47)	1.29 (1.24-1.34)
Carbamazepine	127	275	622	0.66 (0.48-0.90)	183	193	474	0.83 (0.64-1.08)	0.75 (0.62-0.92)
Lithium	432	572	1,048	0.91 (0.78-1.05)	566	770	1,358	0.73 (0.64-0.84)	0.81 (0.73-0.89)
Lamotrigine	688	1,113	1,922	0.76 (0.67-0.86)	975	1,304	2,126	0.93 (0.83-1.04)	0.85 (0.78-0.92)
Valproic acid	955	1,152	1,989	0.88 (0.78-0.98)	244	346	461	0.95 (0.78-1.17)	0.89 (0.81-0.99)

PYs – person-years, aHR – adjusted hazard ratio

Table 4 Risk of hospitalization due to affective disorders associated with specific antidepressants (compared with non-use of antidepressants) and antipsychotics (compared to non-use of antipsychotics) in Finnish and Swedish cohorts and in fixed-effect meta-analysis

	Finnish cohort		Swedish cohort		Fixed-effect meta-analysis aHR (95% CI)
	Events	**aHR (95% CI)**	**Events**	**aHR (95% CI)**	
Antidepressants					
Bupropion	125	0.65 (0.49-0.86)	213	0.73 (0.60-0.88)	0.70 (0.60-0.82)
Vortioxetine	68	0.80 (0.55-1.16)	111	0.78 (0.59-1.03)	0.79 (0.63-0.98)
Venlafaxine	2,185	0.87 (0.79-0.96)	1,337	0.94 (0.84-1.05)	0.90 (0.84-0.97)
Sertraline	617	0.75 (0.64-0.87)	1,310	1.01 (0.91-1.13)	0.92 (0.84-1.00)
Amitriptyline	132	0.97 (0.73-1.28)	172	0.90 (0.70-1.16)	0.93 (0.77-1.12)
Paroxetine	271	0.88 (0.70-1.11)	206	1.09 (0.85-1.40)	0.97 (0.82-1.15)
Duloxetine	398	0.88 (0.74-1.05)	695	1.07 (0.94-1.22)	1.00 (0.90-1.11)
Escitalopram	908	0.95 (0.84-1.09)	879	1.04 (0.92-1.17)	1.00 (0.91-1.09)
Fluoxetine	357	1.01 (0.83-1.22)	682	1.06 (0.92-1.21)	1.04 (0.93-1.16)
Citalopram	800	1.05 (0.91-1.21)	408	1.15 (0.96-1.38)	1.09 (0.97-1.22)
Mirtazapine	1,334	1.08 (0.96-1.21)	1,203	1.17 (1.06-1.30)	1.13 (1.04-1.22)
Non-use of antidepressants	4,115	Reference	5663	Reference	Reference
Antipsychotics					
Any LAI	32	0.38 (0.22-0.64)	51	0.77 (0.52-1.13)	0.60 (0.44-0.82)
Clozapine	73	0.61 (0.44-0.85)	40	0.61 (0.38-0.98)	0.61 (0.47-0.80)
Haloperidol	58	1.55 (1.01-2.37)	128	0.71 (0.54-0.92)	0.88 (0.70-1.10)
Quetiapine	3,066	0.87 (0.80-0.95)	1,492	1.02 (0.93-1.11)	0.94 (0.88-0.99)
Perphenazine	299	0.96 (0.79-1.18)	46	0.81 (0.49-1.32)	0.94 (0.78-1.13)
Olanzapine	1,649	0.96 (0.86-1.06)	1,963	0.98 (0.90-1.07)	0.97 (0.91-1.04)
Levomepromazine	264	0.96 (0.79-1.17)	293	1.06 (0.89-1.26)	1.02 (0.89-1.15)
Aripiprazole	384	1.03 (0.88-1.22)	553	1.01 (0.88-1.15)	1.02 (0.92-1.13)
Risperidone	1,319	1.04 (0.93-1.16)	671	1.02 (0.89-1.16)	1.03 (0.94-1.12)
Antipsychotic polytherapy	2,440	1.01 (0.92-1.11)	1,827	1.11 (1.02-1.21)	1.06 (1.00-1.13)
Flupentixol	55	1.60 (1.02-2.50)	111	1.07 (0.79-1.46)	1.22 (0.94-1.57)
Non-use of antipsychotics	6,004	Reference	10,138	Reference	Reference

aHR – adjusted hazard ratio, LAI – long-acting injectable antipsychotic

combination was not associated with a decreased risk of relapse compared to non-use of both antidepressants and antipsychotics (aHR=1.01, 95% CI: 0.96-1.06).

Benzodiazepine and related drug use was associated with an increased risk of relapse (aHR=1.29, 95% CI: 1.24-1.34) compared to non-use of these drugs. Use of carbamazepine (aHR=0.75, 95% CI: 0.62-0.92), lithium (aHR=0.81, 95% CI: 0.73-0.89), lamotrigine (aHR=0.85, 95% CI: 0.78-0.92) and valproic acid (aHR=0.89, 95% CI: 0.81-0.99) was associated with decreased risk of relapse compared to non-use of mood stabilizers (see Table 3). There were no major changes in these results when the first 30 days were removed from all exposures (see supplementary information).

As to the secondary outcome, i.e. hospitalization due to affective disorders, the same antidepressants were associated with a decreased risk, namely bupropion (aHR=0.70, 95% CI: 0.60-0.82), vortioxetine (aHR=0.79, 95% CI: 0.63-0.98) and venlafaxine (aHR=0.90, 95% CI: 0.84-0.97) when compared to non-use of antidepressants (see Table 4). Mirtazapine was associated with an increased risk (aHR=1.13, 95% CI: 1.04-1.22). Compared to non-use of antipsychotics, any LAI (aHR=0.60, 95% CI: 0.44-0.82), clozapine (aHR=0.61, 95% CI: 0.47-0.80) and quetiapine (aHR=0.94, 95% CI: 0.88-0.99) were associated with a decreased risk (see Table 4).

DISCUSSION

This is the first study to investigate the comparative effectiveness of antidepressants and antipsychotics, and their combinations, in the maintenance treatment of PD. Our results from two nationwide cohorts, including 33,014 patients, indicate that bupropion, vortioxetine, venlafaxine, any LAI, clozapine, the combination of an antidepressant with a weak D2-blocking antipsychotic, and a few specific antidepressant-antipsychotic combinations (namely, amitriptyline-olanzapine, sertraline-quetiapine and venlafaxine-quetiapine) are associated with a decreased risk of relapse. The aggregate groups of any antidepressant, any antipsychotic, and any antidepressant-antipsychotic combination are not associated with lower risk of relapse, and some specific drugs are associated with an increased relapse risk, which underlines the importance of choosing treatments carefully, rather than regarding all of them as "equivalent". The finding that some antidepressants as monotherapy are associated with a decreased risk of relapse is not in line with recommendations from clinical guidelines stating that PD should be treated with an antidepressant combined with an antipsychotic[18,19], although these guidelines do not provide specific recommendations on relapse prevention.

The results regarding bupropion may seem surprising, as this drug inhibits the reuptake of dopamine and noradrenaline and increases dopamine synaptic levels. There have been case reports of bupropion-induced psychosis, but, according to a systematic review, bupropion is safe to use in patients with schizophrenia, and the risk for bupropion-induced psychosis seems negligible[20]. The clinical picture of PD – especially among the most severely ill patients – often resembles the motor retardation phenotype seen in catatonic schizophrenia. Since catatonic schizophrenia is associated with decreased rather than increased dopaminergic neurotransmission[21], the enhancement of dopamine activity by bupropion may be beneficial in the treatment of PD, although this is just a hypothesis which requires specific testing.

Our finding of a decreased relapse rate with venlafaxine is in line with a Cochrane review[22]. To our knowledge, there are no previous data on vortioxetine, while some preliminary evidence suggests that this drug may be more efficacious than other antidepressants in depressive episodes associated with schizophrenia spectrum disorders[23]. Vortioxetine is the only antidepressant with substantial 5-HT7 antagonism, and results from animal and human stem cell studies suggest that antagonists of 5-HT7 receptors may be efficacious in psychosis[24,25].

Clozapine was the only oral antipsychotic associated with a decreased risk of relapse. This is the most effective antipsychotic in the treatment of schizophrenia[26], including for depressive symptoms[16]. Furthermore, it has unique effects on the prevention of suicide attempts and completed suicides[27,28]. The use of any LAI was also associated with a decreased risk of relapse. These preparations have been associated with better treatment outcomes than oral antipsychotics in several real-world studies of schizophrenia and bipolar disorder[14,15,29]. Non-adherence to antipsychotic treatment is an issue also in PD, and this may explain the effectiveness of LAIs in this condition.

A decreased risk of relapse was associated with the use of some specific antidepressant-antipsychotic combinations – namely amitriptyline-olanzapine, sertraline-quetiapine and venlafaxine-quetiapine – compared to non-use of antidepressants and antipsychotics, which is in line with the finding that the combination of an antidepressant with a weak D2-blocking antipsychotic is beneficial. However, these exploratory analyses of antidepressant-antipsychotic pairs may have lacked statistical power.

The very commonly prescribed citalopram and escitalopram were not associated with a decreased risk of relapse, which suggests that they should not be used in PD. For mirtazapine, it could have been hypothesized that the observed increased relapse risk was caused by its frequent use for insomnia, at doses lower than effective antidepressant ones. However, this was not the case, as the result in the Finnish cohort (where dose modelling was available) did not change when we excluded low-dose mirtazapine use from the analyses.

Benzodiazepine use was associated with an increased risk of relapse, also when the first 30 days were removed from analyses. By contrast, carbamazepine, lithium, lamotrigine and valproic acid all showed a decreased risk, although country-specific results were more heterogeneous, perhaps due to lack of statistical power. These results should encourage utilization of lithium and other mood stabilizers as adjunctive medications, and discourage the use of benzodiazepines in PD.

The strengths of our study include consistent nationwide data from two countries, with large cohorts and a long follow-up. The same methodology was applied for cohort identification from similar registers in the two countries. Exclusion criteria, exposure and drug use modelling, outcomes and analyses were also the same. Moreover, we utilized within-individual models to minimize selection bias.

This study has some limitations, which are inherent to the data sources used, most notably a lack of randomization and of detailed clinical data (for instance, we could not account for the use of electroconvulsive therapy and psychotherapies). Moreover, we lacked data on the duration of psychotic symptoms, and whether or when patients were in remission. Some antidepressant-antipsychotic combinations lacked statistical power. Finally, residual confounding may exist in the between-individual analyses, related to, for example, severity of illness or symptoms. It is, however, noteworthy that the results of the sensitivity analyses, where the first 30 days were removed from all exposures, of between-individual analyses, of analyses where people transitioning to bipolar disorder or schizophrenia were removed, and of analyses with random effects meta-analysis (with exception of LAIs) were in line with the main results.

In conclusion, our results challenge the current recommendation in clinical care guidelines of combining antipsychotics and antidepressants as a standard treatment strategy in PD, at least when used for relapse prevention. These findings also encourage choosing specific antidepressants and antipsychotics carefully for the maintenance treatment of PD, as most drugs were not associated with a decreased risk of relapse, and some commonly used antidepressants were actually associated with an increased risk. Beneficial results with LAIs may imply that adherence to antipsychotics is a problem in real-world circumstances, and should be carefully monitored and enhanced among patients with PD.

ACKNOWLEDGEMENTS

This study was funded by the Finnish Ministry of Social Affairs and Health through the developmental fund for Niuvanniemi Hospital. H. Taipale was supported by the Academy of Finland (grants 315969, 320107, 345326) and the Sigrid Jusélius Foundation. This project utilized data from the REWHARD consortium supported by the

Swedish Research Council (grant 2021-00154). The funders had no role in the design and conduct of the study; the collection, management, analysis and interpretation of data; the preparation, review and approval of the manuscript; and the decision to submit the manuscript for publication. Supplementary information on the study is available at https://www.niuva.fi/wp-content/uploads/2023/11/taipale-real-world-effectiveness-of-ads-and-aps-for-psychotic-depression-supplement.pdf.

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DOI:10.1002/wps.21205

R. Spitzer and the depathologization of homosexuality: some considerations on the 50th anniversary

Fifty years ago, in what is arguably the most socially momentous decision in the modern history of psychiatry, the American Psychiatric Association (APA) removed homosexuality as a category of mental disorder from its official Diagnostic and Statistical Manual of Mental Disorders (DSM), then in its second edition (DSM-II). Although removal is often dated to the APA Board of Trustees' vote in December 1973, that vote was actually challenged, and removal was finalized in a referendum in April 1974. Rather than awaiting the DSM-III, the change was made immediately in the next printing of the DSM-II.

The elimination of homosexuality as a category of psychiatric disorder depended on many people, including courageous gay activists as well as sympathetic psychiatrists and APA officers. However, the primary architect and moving force behind removal was R. Spitzer (1932-2015), who played a unique role both intellectually and politically[1,2]. Moreover, Spitzer's arguments justifying removal continue implicitly to shape the DSM today, a legacy worth making explicit.

Spitzer, a member of the APA's Nomenclature and Statistics Committee that produced the DSM-II in 1968, took a leadership role in confronting the homosexuality issue even though he had no fixed opinion at the start. In late 1972, he attended a conference session on aversive behavioral treatment of homosexuality, during which gay activists protested against the categorization of homosexuality as a mental disorder. He invited them to present their case to the Nomenclature and Statistics Committee, and promised to organize a debate on the issue at the next annual APA meeting.

In February 1973, a group of gay activists presented their arguments to the Committee. The main speaker was C. Silverstein, a clinical psychologist who, rather than simply attacking psychiatry for the harm that the diagnostic category was doing to gays by justifying persecutory laws, tried to address the issue in professionally relevant terms. He pointed to lack of evidence for increased psychological problems among gays, offered examples of questionable psychiatric categories in the past, and argued that the psychiatric diagnosis of homosexuality was just society's moral judgment dressed up as medicine[3]. Nevertheless, the Committee remained largely unpersuaded regarding removal.

Keeping his promise, Spitzer organized and chaired a debate on homosexuality at the APA's May meeting in Honolulu. Afterwards, R. Gold – a gay activist on the panel[4] – took Spitzer to a secret meeting of the "Gay-PA", an organization of closeted gay psychiatrists. Spitzer was struck by this group of high-functioning colleagues and, in light of his recent thinking about the concept of mental disorder and the nature of psychiatric diagnosis, he was finally convinced that it made no sense to label their condition a mental disorder. Within weeks, he submitted to the Nomenclature and Statistics Committee a position statement proposing that the category of homosexuality be eliminated from the DSM and offering a conceptual rationale for doing so.

When the Committee refused to endorse his proposal, Spitzer forwarded the unendorsed proposal to higher levels of the APA hierarchy anyway. He also drafted a policy statement declaring that the APA supported civil rights for gays, which the Committee did endorse. In December 1973, both the proposal for removal and the civil rights statement were passed by the APA's Board of Trustees. During the subsequent referendum, when it looked like the Trustees might be overruled, Spitzer drafted a letter detailing the arguments for removal and had it sent out to all APA members.

Spitzer's rationale for removal consisted of a proposed requirement for mental disorder and an argument that homosexuality did not satisfy that requirement. Specifically, Spitzer proposed: "For a mental condition to be considered a psychiatric disorder, it must either regularly cause subjective distress, or regularly be associated with some generalized impairment in social effectiveness or functioning"[5]. If the impairment was not generalized but limited to one area, that must be judged an "important" area of functioning, which – Spitzer acknowledged – involves a value judgment[6,7]. This logical approach cut through the many inconclusive arguments and counterarguments on both sides. It also addressed Spitzer's other preoccupation to counter the anti-psychiatric position that there is no such thing as mental disorder. He pointed out that psychoanalysis had influenced psychiatry to label any non-optimal functioning as disorder, but disorder has a narrower meaning, requiring a condition to be significantly harmful in the form of distress or impairment[8].

Spitzer argued that what is important is the ability to have satisfying intimate sexual and emotional relations with another person, but that whether the person is of the same or a different sex is not important. Thus, homosexual individuals are not impaired. However, if distressed, they could qualify as disordered. Consequently, when homosexuality was removed, another category – "sexual orientation disturbance" in the DSM-II or "ego-dystonic homosexuality" in the DSM-III – was added to the manual for homosexual individuals distressed by their sexual orientation. Spitzer's analysis allowed him to retain the categories of sexual paraphilias because, he argued, they all impair the ability to experience satisfying intimate sexual and emotional relations with another person.

Clearly, a great many homosexual individuals were distressed due to social persecution or because of "internalized homophobia", i.e., accepting and internalizing negative social judgments. Spitzer blocked that kind of distress from indicating disorder status by requiring that, in order to qualify as mental disorder, the condition should be "intrinsically associated with subjective distress", meaning that "the source of the distress or impairment in functioning must be the condition itself and not the manner in which society reacts to the condition"[8].

The removal of homosexuality is a long-settled historical episode, but Spitzer's rationale is still influencing us. The notions of distress and impairment as Spitzer used them did not appear in the DSM-II, but were introduced into the DSM-III as a result of Spitzer's analyses and have played multiple roles since. Spitzer's "distress or impairment" criterion was incorporated into the DSM's definition of mental disorder: "Mental disorders are usually associated with significant distress or disability in social, occupational, or other important activities". In the DSM-IV, to reduce implausibly high prevalence rates of mental disorders emerging from epidemiological surveys, the "clinical significance criterion" was added as an additional diagnostic requirement in most major diagnostic categories. For example, the diagnosis of major depressive disorder requires that "the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning". The notion of "significant" or "clinically significant" distress or impairment appears to be a stand-in for Spitzer's idea that the degree of harm must be above some substantial threshold and not just a matter of non-optimality.

Spitzer's idea that a condition itself might not be a disorder *per se*, but that an individual's distress about having the condition might be a disorder, finds several manifestations in the DSM-5-TR. For example, "gender identity disorder" in the DSM-IV was renamed "gender dysphoria" in the DSM-5, which "focuses on dysphoria as the clinical problem, not identity *per se*", to suggest that those undistressed by gender identity incongruence do not have a disorder.

In sum, fifty years after Spitzer's conceptual resolution to the homosexuality dispute, the fruits of his analysis have penetrated into many areas of our diagnostic manuals. Yet, the analysis leaves us with unfinished business in sorting out the meanings of distress and impairment, and in acknowledging and clarifying the challenging value judgments that inevitably are involved in diagnostic decisions[9].

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DOI:10.1002/wps.21206

Standards for randomized controlled trials of efficacy of psychological treatments

The randomized controlled trial (RCT) is the gold standard of evidence for health interventions, including psychological treatments such as psychotherapies. Indeed, an evidence-based treatment is defined as having two or more high-quality supporting RCTs.

RCTs of psychological treatments share many of the basic methods with pharmacological RCTs, including clear definition of the participant sample, randomization to an experimental or control condition, and standardized assessment that is consistent across treatment arms. However, there are some unique challenges to RCTs of psychological treatments, including specifications for the control condition, treatment integrity procedures, and issues related to trials of digital interventions.

The control condition aims to remove the effects of threats to internal validity, such as the natural course of the target condition, the effects of research procedures, and statistical artifacts such as regression towards the mean, thereby enhancing confidence that the outcome of the trial can be uniquely attributed to the experimental condition. While the pill-placebo is an elegant standard for pharmacological RCTs, there is no predominant solution for RCTs of psychological treatments.

There are many forms of control conditions for these latter RCTs, including no-treatment and waitlist conditions, treatment-as-usual, conditions that provide a portion of the experimental treatment such as attention controls, and active comparators that provide another validated treatment. The choice of control condition is guided first and foremost by the scientific question. The RCT evaluates those treatment elements that are unique to the experimental condition, since the treatment elements common to both the experimental and control conditions are washed out through randomization. If the question is whether or not a treatment can improve outcomes relative to what is currently done, treatment-as-usual may be appropriate, if defined correctly[1]. If the question is whether a specific set of treatment procedures is effective, an active treatment that controls for all other treatment processes may be more appropriate.

One challenge is that control conditions themselves have different effects on the outcome, some obvious and some less obvious[2]. The larger the effect of the control condition, the smaller the difference between the control and experimental treatments. For example, control conditions that include an active treatment (e.g., attention control or alternative treatment) will likely produce large effects, and consequently smaller differences between the experimental and control treatment. Control conditions with little or no treatment (e.g., no-treatment control) produce smaller changes in outcome, thereby resulting in larger between-treatment effects.

However, control conditions may also produce inadvertent or unexpected effects. For example, two meta-analyses have found that waitlist controls produce significantly smaller improvements compared to no-treatment conditions, and thereby larger effects for the experimental treatment relative to the control condition[2,3]. One possible explanation for this is that participants assigned to a no-treatment condition recognize that they will not get treatment and search for other solutions to their problems, while waitlist control conditions shut down natural help-seeking behaviors. Participants assigned to a waitlist condition expect that treatment will come and consequently do what the researchers ask – they wait. Thus, seemingly similar control conditions can produce dramatically different results.

Several decision-making frameworks for control condition selection have been proposed[4,5]. Generally, these frameworks suggest that earlier phase RCTs that are piloting an intervention should use control conditions that have less of an effect, because the greatest threat to the public good in early phases is killing off the innovation of promising treatments. Later phase RCTs should be more rigorously controlled, as it is critical to protect patients, providers and payers from ineffective or dangerous treatments.

The experimental treatment should be clearly defined by a specific manual. Treating clinicians should be trained and supervised, and the fidelity of treatment administration should be monitored. While these treatment integrity procedures are usually applied to experimental interventions, many RCTs do not apply them to control treatments. A meta-analysis found that RCTs that do not manualize the control treatment, provide less training and supervision to control treatment therapists, or do not conduct fidelity monitoring of the control condition, produce significantly larger between-treatment effect sizes than RCTs that apply all of these procedures equally across treatment arms[2]. Thus, all research procedures should be applied equivalently across treatment arms, including treatment integrity procedures.

The outcomes achieved in rigorously controlled RCTs are usually diminished in clinical practice. This phenomenon, referred to as "voltage drop" or research-to-practice gap[6], is common across medicine, but has some unique considerations in psychological treatments. Many of the research procedures necessary to ensure internal validity reduce generalizability. For example, treatment integrity processes are quality controls that can strengthen treatment potency but are not processes that commonly exist in real-world settings. Subsequent implementation trials are necessary to evaluate the effects of a treatment under real-world conditions[7].

Over the past two decades, there has been a dramatic growth in the number of RCTs evaluating digital mental health interventions, delivered via smartphone apps or websites. These interventions can be deployed as fully automated (without any human support), coached or guided (including some low-intensity human support from a therapist or coach), or as an adjunct to standard treatment. Because a digital mental health intervention is clearly defined through the software code, treatment integrity measures are not needed for the digital portion of the intervention. While treatment integrity procedures are still recommended for the human support components, this support is typically much less complex than psychotherapy, and therefore simpler to manage and potentially more generalizable. Control treatment definition and selection poses similar challenges to those described above, with additional possible control elements including receipt of a sham or alternative app.

Traditional RCT methodology requires that the treatment be held constant throughout the trial, so that it is clear exactly what is being evaluated. In contrast to medications, which do not change at all, and psychotherapies, in which the treatment manuals remain constant, apps change frequently. Once an RCT is completed, an app is likely to be changed before being released and will continue to be modified thereafter. Thus, we argue that RCTs should test the treatment methods and principles of digital mental health interventions rather than the products themselves, as the product will continue to evolve as long as it is available and supported.

Trials of intervention principles (TIPs)[8] allow the experimental app to be iteratively improved during the trial by incorporation of new learning, thus reflecting the dynamic nature of digital technologies. A principle statement is articulated *a priori*, and is used to constrain any iterative changes made during the trial, thereby maintaining internal validity. In accordance with the CONSORT-EHEALTH reporting guidelines, any such changes to the app should be documented and reported, allowing transparency[9]. While TIPs articulate a solution to challenges posed in the evaluation of digital mental health interventions, how evidence is defined for digital products that continually evolve remains an area of debate.

In summary, well-controlled RCTs of psychological interventions are necessary for the protection of all stakeholders, including patients, from ineffective treatments. Considerations unique to RCTs for psychological interventions include the definition of control conditions and ensuring that treatment integrity procedures are consistent across treatment arms. With the growing number of RCTs for digital mental health interventions, RCT methodologies must further adapt to take into consideration the evolving nature of digital technologies, which may include methods allowing iteration of the experimental app during the trial.

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DOI:10.1002/wps.21207

The future of dynamic networks in research and clinical practice

A problem attracts other problems[1]. An individual having one symptom (e.g., feelings of sadness) often will have more symptoms over time (e.g., sleep disturbances). The observation that symptoms generate other symptoms has led to the highly influential psychopathological network theory, in which the focus is on how mental disorders can be seen as networks of interacting symptoms[2]. In such psychopathological networks, symptoms are the nodes, and the connections between them are termed edges.

The network theory posits that individuals can have different symptom networks, which can also change within a single person over time. Not only are the symptoms in the network likely to be different between individuals; the connections between the symptoms are also likely to differ. Whereas for person A having sleep disturbances may trigger suicidal thoughts, this may not be the case for person B. Subsequently, a central notion stemming from network theory is that interventions should not only target symptoms, but also the connections between them, breaking the vicious cycle.

In clinical research and practice, networks for patients are often inferred from time series data based on symptom and/or emotion questionnaires that are administered several times a day over, for instance, a time period of several weeks. Networks based on such data have been called *person-specific dynamic networks*. Even though the models used for inferring these dynamic networks are not new, what is new is the visualization of these models, which makes network modelling appealing and tangible for both research and clinical practice[3].

What is often overlooked in the field is the need to bridge the gap from an insightful theory to an actual model. To get from a network theory to a model there are, broadly speaking, two steps that need to be made. The first step concerns the kind of data to be collected from the patient, and the second regards the modeling of these data in such a way that it does justice to the theory.

Thus, the first step to a dynamic network model is collecting and selecting the necessary data. In the network theory, the focus has been on symptoms and emotions, and thus most person-specific dynamic networks almost exclusively include symptoms and/or emotions items. However, further behavioral, context and cognitive items could be included in the networks[4]. Emotions and symptoms indicate how a patient is doing, whereas behavioral, context and cognitive items can lead to insights on why the patient is feeling a certain way. This can help in targeting therapeutic interventions, for example, by indicating behaviors, social contacts or thoughts that lead to feelings of sadness. Additionally, these items should be formulated and personalized in terms of content in collaboration with the patient, which can result in a higher chance of capturing crucial aspects of his/her daily life, and better reflect his/her interests and experiences in general[5].

Other sources than questionnaire data should also be considered, such as social media, passive sensing, and many other available kinds of time series data. Collection of passive sensing data (e.g., location tracking of mobile phones) can lead to reduction of the burden on the patient, as the data are gathered automatically. In addition, it can provide new therapeutically relevant insights complementing questionnaire data. For example, if a patient with social anxiety indicates in a questionnaire that she followed a lecture, it is not clear from this whether she had a breakthrough and actually went to campus, or watched the lecture online at home, but location tracking data can provide this complementary information.

After the source of data has been chosen, a model needs to be identified to infer the network. With regard to this second step, models based on vector autoregression are the most commonly used to infer these person-specific networks. A vector autoregressive model allows to study, for instance, reciprocal predictive effects: does stress predict one's sadness at the next time point, the other way around, or are both stress and sadness predictive of each other?

Although this model does justice to the dynamic structure of data, it is too limited to capture all aspects of the network theory. In fact, it cannot deal with change in the network, whereas this is often one of the main elements of interest (e.g., did the mood of the patient improve and why?). Furthermore, different variables measured at different time scales (e.g., sleep quality vs. mood) cannot be modeled simultaneously, meaning that often factors such as sleep quality (measured once a day) are not taken into account into the network, even though they are known to affect one's mood (mood is often measured several times a day). Additionally, these models are very data hungry, meaning that many time points (more than 100 per individual) are often needed to model all relevant variables in the network[6].

Beyond the many different choices that one could make in the pursuit of a network model, one could also take a different direction altogether. Network theory itself is not tied to any model, nor to a number of variables. Thus, fitting a vector autoregressive model on all relevant variables to infer a dynamic network is neither necessary nor *per se* advisable, as including more variables but not increasing the number of time points will only decrease the accuracy of the estimated network[7].

Instead of the rather ambitious and broad goal of trying to unravel the dynamic processes between symptoms, a more viable approach could be to test specific and targeted questions, which often emerge naturally between patient and therapist (e.g., in functional analysis)[8]. Studying the relation between only two variables can already be of interest: for example, studying whether a specific physical activity leads to a positive change in one's sleep pattern. This is still in line with the network theory (how do variables influence each other), but, given the focus on change, should not be studied with the standard vector autoregressive model[9]. Rather, it could be studied with, for instance, regime-switching models. With these models, one could investigate whether there are different regimes in the data, and whether the regime of more physical activity (vs. less physical activity) is associated with a positive change in one's sleep pattern[4]. In general, different questions might require different (network) models. Therefore, a broadening of our available arsenal of statistical techniques is also essential to optimize the move from network theory to an actual model.

To summarize, we see that until now dynamic networks have been implemented in a rather restrictive way, in which often only specific variables and one specific model are commonly used. Importantly, the network theory puts no constrains on the data and the model used to come to a person-specific network. This means that in the future we do not have to hold on to specific data or models. In the end, researchers and clinicians alike should explicate how they want to apply the network theory to the specific patient and situation, and then consider what kind of data and model is best suited for that purpose.

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DOI:10.1002/wps.21209

The promise of social recovery therapy in non-affective psychoses

Non-affective psychoses (schizophrenia and schizophreniform disorders) are the health conditions of working age adults most frequently associated with poor social outcomes. Long-term follow-up studies suggest that less than 50% of people with these conditions achieve social recovery, less than 15% achieve sustained recovery in both symptomatic and social domains, and only 10-20% of people return to competitive employment, despite the majority reporting that they wish to work[1].

Social recovery therapy (SRT) is a psychosocial treatment to promote social recovery in people with non-affective psychosis who are socially withdrawn, have complex and comorbid problems, and are unresponsive to existing interventions. It is based on a model in which social disability evolves as a result of lifestyle patterns of low activity, adopted to achieve behavioral avoidance, and maintained by lack of hope, agency and motivation.

Social disability in psychosis typically occurs in the context of persistent positive and negative symptoms and cognitive impairment, often accompanied by depression, anxiety and other psychopathological manifestations. Alongside such issues are complex social circumstances and systemic issues, including problematic family dynamics, victimization, social threat and social deprivation. In the face of such problems, individuals adopt lifestyle patterns of extreme social withdrawal, leaving work or education and losing contact with social networks.

SRT is described in a manual[2] and delivered individually across 9 months. Sessions take place in participants' homes and community locations. Interim telephone and email contact usually occurs. SRT delivery is structured in three stages. Stage 1 includes assessment and development of a shared social recovery formulation. Stage 2 involves identifying and working towards medium- to long-term goals guided by a systemic formulation of barriers to recovery, with a focus on promoting a sense of agency, hope and motivation, and encouraging activity while managing psychotic symptoms. Stage 3 involves the active promotion of structured activity linked to meaningful goals, while still managing symptoms.

The focus of the intervention is on the individual's personal values and goals, identifying problems and barriers to these, then promoting hope for meaningful behavioral change and activity toward these goals. There is a strong emphasis on the use of behavioral strategies (including behavioral experiments, graded exposure and behavioral activation) to overcome avoidance and promote meaningful lifestyle change *in vivo* whilst managing symptoms as necessary to implement a concrete pathway to social recovery. Evidence and experiences from this behavioral work are used to further instill hope and promote positive beliefs about self as the individual works towards achieving meaningful change in his/her life.

As SRT aims to engage people with psychosis into structured activity, it often includes supporting them to access employment, education, training, voluntary and/or leisure opportunities. Much of SRT takes place in community settings. It is often useful for the therapist to drive the client to new locations and settings or accompany him/her on public transport.

To achieve gains in social recovery against a background of often years of withdrawal and social disadvantage means that therapists have to integrate techniques typically associated with assertive community treatment and supported employment. Working systemically with families and stakeholders surrounding the individual to promote opportunities in the social environment is also important. Behavioral activation and behavioral experiments are conducted in line with the client's identified goals and values and at a pace respecting the nature of the difficulties faced. The therapist works alongside the client to aid motivation and engagement in identified activities that can be incorporated into daily life, and work out collaborative strategies to manage ongoing symptoms *in vivo*.

To date, we have conducted two assessor-blind randomized controlled trials of SRT in people with psychosis with severe social disability.

In the Improving Social Recovery in Early Psychosis (ISREP) trial[3], 77 participants with affective or non-affective psychosis presenting social withdrawal were randomized to receive either SRT plus treatment-as-usual (TAU) or TAU alone. TAU consisted of case management from a secondary mental health care team. In the non-affective psychosis group, SRT showed a significant and clinically beneficial effect on the primary outcome of weekly hours in structured activity, as well as on positive and negative symptoms. There was also an effect of SRT on hopelessness and positive beliefs about self, with improvements on these variables being a mediator of the change in structured activity. The intervention was also cost-effective[4].

SUPEREDEN3[5] was a larger (N=154) phase 2 trial aimed to enhance social recovery in patients who had not responded to early intervention service (EIS) treatment, by combining standard EIS provision with SRT. The primary analysis indicated that the SRT plus EIS was associated with an average increase in structured activity over 8 hours per week greater than EIS alone (95% CI: 2.5-13.6; p=0.005). The size of the effect represents an amount of activity equivalent to a full working day.

There is evidence from both the above trials that the gain from SRT may be maintained 6 months beyond active treatment. In a further separate longer-term follow-up study on the ISREP group[6], none of the 24 cases in the TAU group had engaged in paid employment in the year following the end of the intervention period, compared with 5 out of 20 (25%) cases in the SRT+TAU group.

SRT offers most promise in promoting social recovery in complex cases of non-affective psychoses in which there is little evidence of response to other interventions. Although the results from the two available randomized controlled trials are positive, further large scale pragmatic studies are needed, possibly being expanded to more chronic cases. There may also be promise in combining SRT approaches with other psychosocial interventions, such as cognitive remediation therapy[7].

We designed SRT so that it can be delivered in task-sharing formats by a less costly and more widely available workforce than that involved in the above trials. We have now developed extensive training materials, including videos as well as adherence and supervision guidance, which we have collated on a website[8]. Through this and related work, we have found that it is possible to train "non-expert therapists" in key elements of the SRT approach, which can then be successfully implemented following the manual.

What is needed in the future is to build on the promise of the existing trials of SRT toward further research and implementation involving non-expert therapists and extending into wider populations of people with non-affective psychosis in the community.

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DOI:10.1002/wps.21208

The aggregation of marginal gains: a pragmatic philosophy of clinical care in psychiatry

The cliched opening sentence of many articles in the psychiatric field bemoans the limited efficacy of individual treatments. However, this singular truth is far from the whole truth. The theory of aggregation of marginal gains, also known as the "1% improvement theory", suggests that small, sustained, incremental improvements in multiple areas can lead to substantial overall progress in a given field[1]. This theory has been applied in various areas, including sports, business, and health care, and appears to be relevant to psychiatric clinical practice.

This approach was famously adopted by the Sky British Cycling Team. The team's management implemented multiple small changes and improvements to diverse aspects of the team's operations, including training, nutrition, sleep, equipment and recovery. The goal was to combine these individually small improvements to achieve a significant overall increase in performance. This alchemy successfully transmuted leaden failures into golden victories in the Tour de France. The concept of "aggregation of marginal gains" has since been widely adopted in other fields, and has become a popular approach to achieving continuous improvement[1]. This notion is concordant with the view of Stein et al, put forward recently in this journal[2], that progress in psychiatry will likely not be driven by a singular transformative paradigm, but by "incremental progress and iterative integration".

An approach to the aggregation of marginal gains in psychiatry can be based on the concomitant utilization of interventions that target specific risk factors or operative pathways for an individual. As argued by Kendler[3], psychiatric disorders are highly multicausal, with as many as 37 potential risk factors identified, for instance, for depression. Additionally, Borsboom et al[4] show that the complex network interaction of multiple factors results in complex psychiatric syndromes, which cannot be explained by reductionist models.

Similarly, Loscalzo and colleagues[5] used the mathematics of networks to show that the interactions between all relevant factors (the "interactome") and all the changes that can lead to a diseased state (the "diseaseome") form stable networks. These networks, when perturbed by therapeutic interventions, will adapt and can lead to a healthy state (the "healthyome"). However, this healthy state tends to be temporary, and the network will tend to revert to the diseased state "unless multiple interventions lock the network into the healthy state"[5].

Furthermore, by modelling those factors which cause other factors (e.g., insomnia can cause fatigue), clinicians can identify the most important areas to target interventions[2]. Here, the "Swiss cheese" model of risk mitigation[6] can be illustrative of a path forward. Widely used in the public health sphere, such an approach focuses on incremental improvements across several imperfect interventions to provide a sum effect greater than any one intervention alone.

Attempts to conceptualize and manage psychiatric disorders as monocausal or simply linear have generally been unsuccessful. By extension, approaches that leverage the above multicausal complex network models into treatment are now needed. This also has the potential to pragmatically personalize therapy. Precision medicine approaches have largely focussed on biomarkers and other singular factors capable of stratifying care. In contrast, clinical formulation aims to understand and explain the diversity and network of multiple predisposing precipitating and perpetuating factors leading to an individual's problems and symptoms[7]. These span genetic loading, different etiological factors for those with earlier or later age of onset, the impact of early or ongoing life events and stressors, lifestyle and environmental factors; comorbid substance use, medical or psychiatric conditions; early life experiences, development and subsequent cognitive schemas, personality strengths and difficulties, and current relationships and supports[7,8].

Merging the constructs of aggregation of marginal gains and complex clinical formulation is a pragmatic way to identify an individual's risk pathways and combining the multitude of possible and available treatments.

Furthermore, a subtractive approach focuses on eliminating factors that might be detrimental to care. Two potentially malleable factors include the treatment gap, whereby individuals with disorders do not have access to care, and the evidence-practice gap, which refers to the gap between treatment received and the evidence base[2]. Health care systems are complex interconnected chains, with disruption at any link capable of adversely impacting clinical outcomes. A continuous improvement approach involves regularly evaluating the patient's progress and iteratively identifying new areas for improvement. By continuously making small systems-level and individual improvements and adjusting the treatment plan as needed, clinicians can help their patients make ongoing progress in their health.

Lifestyle factors operate across the spectrum of psychiatric and non-communicable physical disorders. There is now abundant evidence that smoking increases the risk for several psychiatric disorders and worsens outcomes; there is equal evidence that smoking cessation, previously thought of as too difficult, represents a clinical low-hanging fruit, being associated with improvement in many domains of mental health. The same is true of increased physical activity, improved sleep and diet, and reduced screen time: improvements in these domains are associated with better outcomes in multiple mental health and comorbid physical disorders. Moreover, pharmacogenomic testing might produce a marginal gain for a subgroup of people, as may digitally augmented phenotyping and therapies[2].

In addition to their direct effects, diseases and their symptoms erode people's capacity to engage in meaningful, rewarding and purposeful activities. Activity scheduling, encouraging hobbies and activities, supporting occupational engagement, volunteering, and enhancing social networks can increase resilience and supports, as does supporting caregivers and meaningful relationships.

Thus, multidisciplinary approaches focusing on small improvements in various areas can help significantly improve overall health. Seemingly small benefits at a point in time have nevertheless the capacity, through compound interest, to become large benefits over time. Each gain is a small victory that subtly enhances hope and boosts confidence and self-efficacy, which increases the capacity of the individual to take on further tasks. Just as compound interest in investing does not appear to do a lot in the first years, but does a huge amount over decades, each clinical gain amplifies other gains, and increases the possibility of further improvement in a self-reinforcing cycle.

A further and synergistic construct is that of persistence. A recent paper suggested that most people who persisted with up to 10 different treatments showed meaningful clinical improvement [9]. This conclusion is supported by epidemiological data showing that people who received specialized, multi-sector care were more likely to report being helped "a lot"[2]. The obvious caveat is time: the six- or eight-week timeframe of clinical trials is not sufficient for meaningful improvement for most people, and realistic expectations need to be set. Meaningful clinical improvement for most people is generally measured in months, if not years.

In conclusion, the theory of aggregation of marginal gains can be a pragmatic and optimistic philosophy of clinical care. Because of the complexity of psychiatric disorders, there are few silver bullets. By focusing on multiple small, incremental improvements in various areas germane to an individual, clinicians can help their patients progress significantly in their overall mental health. Using clinical formulation to tailor the plethora of available options to the individual's needs, aided by a multidisciplinary and continuous improvement method, clinicians can further enhance the effectiveness of this approach.

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M. Berk is supported by Senior Principal Research Fellowship and Leadership 3 Investigator grants (nos. 1156072 and 2017131) from the Australian National Health and Medical Research Council. W. Marx is funded by a National Health and Medical Research Council Investigator Grant (no. 2008971) and a Multiple Sclerosis Research Australia early-career fellowship. A.A. Nierenberg is supported by the T.P. Hackett Endowed Chair at Massachusetts General Hospital, the Erdman Fund, and the Dauten Family Innovation Fund.

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DOI:10.1002/wps.21174

The NIMH supports more comprehensive and inclusive genomic studies in psychiatry

The inclusion of diverse populations in genomic studies is key to generate more comprehensive findings, as well as to ensure equitable research. However, most genomic studies have been conducted as yet on cohorts of European ancestry, with minimal representation of other populations worldwide[1,2]. To address this historical gap, the US National Institute of Mental Health (NIMH) has established the Ancestral Populations Network (APN), through two funding opportunities[3].

The APN was formed with the overarching goals of: a) accelerating genetic discovery for psychiatric disorders in cohorts of non-European ancestry; b) advancing global mental health discovery and equity; c) facilitating measurement and data analytic harmonization efforts to enhance rigor and reproducibility; and d) generating a resource for network members and the scientific community. The APN also presents a distinctive global perspective toward reducing inequities and disparities in mental health research, by supporting strong in-country leadership representation, strengthening research capacity, and promoting the development of early-stage career researchers.

Overall, the APN will collect and analyze data from 200,000 participants (cases, controls and families) from over 25 sites worldwide, through seven projects.

The Populations Underrepresented in Mental Illness Association Studies (PUMAS) will use the newly developed blended genome exome (BGE) sequencing technology for genetic characterization of severe mental illnesses (SMI), including individuals with schizophrenia spectrum and bipolar disorder, in Africa, South America and the US. The project aims to create the largest to date phenotypic and genomic resource of people with non-European ancestry with SMI data.

The Genomics of Schizophrenia in the South African Xhosa (SAX-II) will characterize the genomic architecture of schizophrenia in the native Xhosa population of South Africa, using a combination of long-read and short-read whole genome sequencing (WGS) methods to identify new classes of damaging mutations. Using these innovative genomic technologies, the project will provide deeper insights into the genomic structure of individuals with schizophrenia and serve as a resource for other case-control comparison studies across ancestral populations.

The Latin American Trans-Ancestry Initiative for OCD Genomics (LATINO) will identify genomic loci for obsessive-compulsive disorder (OCD) in the largest Latin American cohort to date. Genome-wide significant loci will be fine-mapped, and individual polygenic risk scores (PRS) will be calculated to determine genetic liability. The results of this study will provide meaningful insights into the pathophysiology of OCD, possibly leading to more effective treatments and clinical outcomes.

The Identifying the Genetic Causes of Depression in a Deeply Phenotyped Population from South Korea (KOMOGEN-D) will identify genetic variation of a deeply phenotyped (including depression subtypes and environmental influences) cohort of South Korean women with severe recurrent depression. Data from this study will be further meta-analyzed with other cohorts of relevance to enhance the utility of this uniquely created resource.

The Genetic Architecture of Early-Onset Psychosis in Mexicans (EPIMex) will use BGE sequencing to investigate the genetic architecture of early-onset psychosis in a deeply phenotyped (including social determinants of health and environmental exposure measures) pediatric sample in Mexico City, creating the largest resource to date of people with this condition. The project will enhance our understanding of risk factors, with a special focus on the Mexican population, currently underrepresented in psychiatric genetic studies.

The Asian Bipolar Genetics Network (A-BIG-NET) will generate a large-scale genetics resource for the study of bipolar I disorder in East and South Asia populations. Participants from Taiwan, South Korea, India and Singapore will be deeply phenotyped and undergo BGE sequencing, to which data collected from a prior study in Pakistan will be added, to identify new genetic associations and putative causal variants. This resource will provide ways to examine and compare the genetic architecture of bipolar I disorder across other populations worldwide to accelerate efforts in gene discovery.

The Genomics of Autism in Latinx Ancestries (GALA) will investigate the genetic risk of autism spectrum disorder in Hispanic/Latinx ancestry populations, conduct cross-ancestry genome-wide association studies (GWAS) to examine common genetic variation, perform fine-mapping and co-localization analyses of GWAS results, create PRS, and identify rare genetic variants.

The APN provides a unique opportunity to develop areas of high relevance to large-scale genomic studies, including harmonization of clinical and cognitive phenotypes across different sociocultural settings worldwide, the role of social determinants of health, global human research ethics, local research capacity and leadership, and reciprocal knowledge transfer between global settings.

Several workgroups have been established to collaborate in these areas, including: a) a workgroup on phenotype harmonization, aiming to shape the policies and practices for this harmonization, identifying opportunities for aligning phenotype measures across projects, adding new phenotypic measures, and standardizing methods; b) a workgroup on social determinants of health, facilitating discussion about the impact of social determinants of health on genomic research, promoting analyses on the dynamic interplay between genetics and societal factors across different APN projects, and establishing a standard and user-friendly protocol for collecting measures of social determinants; c) a workgroup on ethics, shaping and recommending best practices in community engagement, equity in global collaborations, informed consent and the decisional capacity process, and ethics committee mapping; d) a workgroup on capacity building, shaping the policies and practices that pertain to building human capital by assessing and defining needs, challenges and strengths of the projects in the APN, curating and developing training materials, and suggesting best practices as they relate to equitable collaborations; e) a workgroup on genomic data harmonization, aiming to harmonize ancestrally diverse genomic data to support high-quality data generation across the APN, developing easy-to-use and standardized analytical plans and computational plans across sites, and facilitating the integration of common and rare variant analyses for jointly harmonized genetic analyses; and f) a workgroup on genetic concepts, facilitating and coordinating testing of genetic hypotheses collaboratively across the APN.

Through its collaborative efforts, the APN aims to create a unique resource for the field, with examples and recommendations on how to conduct equitable, global scientific genetic collaborations, as well as outline ethical considerations for establishing new recruitment sites, engaging local communities, and addressing stigma and research hesitancy as they relate to participating in psychiatric genetic research. Further, the APN will provide best practices on culturally adaptive phenotypic transdiagnostic harmonization efforts and integrating phenotypic and genomic data. It will also include recommendations on the collection of measures of social determinants of health and other environmental exposures in mental health genetic studies.

In the genomic space, the APN aims to enhance gene discovery efforts by improving power for common and rare variant discovery, exploring population specific variation, and enhancing trans-ancestry fine-mapping efforts. These, in turn, can facilitate the refinement of PRS transferability between populations, address admixture-related issues, work toward more comprehensive population-specific reference maps, and examine the shared and distinct genetic architecture between different psychiatric disorders and symptoms.

In the training and research capacity space, the APN is taking a psychiatric genetic-focused approach on developing and promoting the next generation of researchers across the world. By including a larger group of diverse populations from across the globe, the APN aims to enhance our understanding of mental illness, which would facilitate the development of new interventions to benefit people of all racial and ethnic groups.

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Further information on the Ancestral Populations Network can be found at https://www.nimh.nih.gov/about/organization/dnbbs/genomics-research-branch/ancestral-populations-network-apn.

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DOI:10.1002/wps.21211

Treatment of substance use disorders in prison settings: statement by the UNODC-WHO Informal Scientific Network, UN Commission on Narcotic Drugs

Since 2014, the United Nations Office on Drugs and Crime (UNODC) - World Health Organization (WHO) Informal Scientific Network (ISN) has brought the voice of science to international drug policy discussions, especially at the Commission on Narcotic Drugs (CND), the drug-control policy-making body of the United Nations (UN). The public health dimension of the world drug problem, including prevention and treatment of substance use disorders (SUDs), has become prominent in policy debates within the UN system[1].

Many people in the criminal justice system have a history of SUDs and other mental health conditions. An estimated one in three people in prison have used drugs during incarceration[2]. The worldwide prison population stands at 11.2 million individuals[3], and continues to increase. This and related prison overcrowding have profound implications for the physical and mental health of people in incarceration and the well-being of their families and communities.

If people with SUDs engage in criminal activities, these are often minor offences driven by the need to support their substance use[4]. Imprisonment is not an effective response to substance use/SUDs[5], and it may exacerbate pre-existing problems. SUDs should be treated as health conditions and not as criminal behaviors. It is essential to provide accessible, evidence-based SUD treatment in the community and establish different non-custodial measures, including SUD treatment as an alternative to conviction or punishment for people with SUDs in contact with the criminal justice system. In case of personal-use-related drug offences and other minor offences by people with SUDs, countries should redirect them toward health care and social services instead of applying ineffective punitive measures.

This approach aligns with the UNODC-WHO International Standards for the Treatment of Drug Use Disorders[4] and the International Drug Control Conventions, the UN Standards Minimum Rules for the Treatment of Prisoners[6], the UN Standard Minimum Rules for Non-Custodial Measures[7], as well as the UN Rules for the Treatment of Women Prisoners and Non-Custodial Measures for Women Offenders[8].

When the severity of the crime precludes the consideration of treatment as an alternative to conviction or punishment, countries need to ensure access to SUD treatment within prison settings and ensure continuity of treatment in line with services provided in the community. Offering treatment and care in prison settings corresponds to the CND resolution 61/7 on "Addressing the specific needs of vulnerable members of society in response to the world drug problem"[9] and the 2016 UN General Assembly Special Session on Drugs Outcome Document[1].

To ensure that people with SUDs in prison settings receive appropriate treatment in line with international standards and guidelines, the ISN recommends the following:

- Individuals who use psychoactive substances for non-medical purposes or have SUDs should not be criminalized for their substance use. People with SUDs, including those in prison settings, should have access to voluntary treatment no matter their legal status.
- Alternatives to conviction or punishment should be provided for people with substance use/SUDs who have committed minor offences, with the aim of reducing crime, recidivism and deaths, and improving health and well-being while enhancing social justice.
- Clinical screening for substance use/SUDs and their comorbidities, notably suicidality prior to and in prison settings, should be provided, to arrive at the correct diagnosis needed to ensure adequate treatment and to prevent the exacerbation of substance use/SUD.
- Care for SUDs should follow ethical guidelines, uphold human rights principles, and align with international standards and norms. It should not be used for punitive purposes.
- Independent review mechanisms, which follow accepted standards, should be established to ensure quality care and ethical treatment in prison settings.
- In all justice-related cases, people should receive treatment and care of a standard equal to that in the community, regardless of gender, age, race, religious, cultural or social status, including programs for individuals with special treatment and care needs.
- Treatment for individuals with SUDs should follow a continuum of care that includes broader health and social services to strengthen success upon return into the community and drug use prevention, especially for children and family members of incarcerated persons.
- Providing treatment for SUDs by prison health services should be clinically independent of prison administrations and yet be coordinated effectively.
- Evidence-based pharmacological treatment should be widely available for the treatment of SUDs in prison and upon return to the community, including for comorbid conditions. Naloxone should be accessible to manage overdoses in criminal justice settings and upon release, and relevant training of professionals and prisoners should be ensured.
- Professional staff training, in health care and justice settings, should be provided to ensure quality care and sustainability.
- Adequate funding should be available to ensure quality care of SUDs before, during and after incarceration.
- Support and investment in systematic data collection should be ensured to monitor, evaluate and allocate resources.
- Recognizing that social determinants of health can be risk factors for substance use and for offending, policies should be developed to address them, as they are equally important for the rehabilitation and recovery of individuals with SUDs.

Treatment for SUDs based on evidence has been shown to be critical in reducing substance use, overdose, reoffending and reincarceration in populations with a history of involvement with the justice system. Treatment and care interventions in line with UNODC-WHO International Standards can contribute towards supporting both the welfare of the community and the promotion of personal recovery. To ensure that all individuals with SUDs who come into contact with the criminal justice system, including those in prison, receive the same level of care, respect and dignity, the ISN is urging UN Member States to change their response to SUDs from a criminal justice to a public health strategy.

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The authors thank C. Gamboa-Riano, H. Fritz, J. Hobin, A. Lee, E. Einstein, E.M. Wargo, and T. Clarke for their valuable editorial work. The authors alone are responsible for the views expressed in this letter, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated. Members of the UNODC-WHO ISN include E. Adjei-Acquah, M. al'Absi, S. Al Emadi, O.A. Alibrahim, P. Arwidson, S. Ben-Ezra, J.G. Bramness, M. Branting, E. Bryun, M. Chakali, C.F. Damin, G. Fischer, E. Krupitsky, R. Lal, C. Leonardi, Z. Liu, M.A. Mahfouz, I. Maremmani, M.T. Matar, S.A. Maua, M.E. Medina-Mora, T. Mota Ronzani, E. Neumeier, I. Obot, S. Onen, K.M. Ostaszewski, P. Roska, M.P. Schaub, O. Scoppetta, V.I. Skriabin, M. Torrens, S.T. Zhenkova, J. Toufiq, G. Vilar, J.A. Villatoro-Velázquez, N. Volkow, K. Vyshinsky and M. Zhao.

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DOI:10.1002/wps.21210

The Serious Mental Illness Management System in China: concerns to be addressed

The Serious Mental Illness Management System (SMIMS) in China is a national government program designed to address the needs of individuals with severe mental illness in the community. The guiding document, Standards for the Management and Treatment of Serious Mental Illness, was updated in 2018[1].

The system aims to provide community-based care to individuals diagnosed with one of the following six mental disorders: schizophrenia, schizoaffective disorder, delusional disorder, bipolar disorder, epilepsy-associated mental disorder, and intellectual disability[1]. It reflects a multifaceted approach, by involving mental health professionals, police, social welfare workers, and volunteers to form community teams.

As of 2020, there were at least 6.4 million patients registered in the system[2]. However, considering the actual number of individuals with severe mental illness in China, the system is likely to have been markedly underutilized. A study found that >50% of people with the above diagnoses were not registered in the system[3].

The SMIMS intends to provide a range of community-based services, including outpatient follow-up, family visits, free medication, and financial assistance. A recent study[4] showed that, among discharged patients with schizophrenia, 88.9% accepted the follow-up management. A few other studies reported that patients in the SMIMS had more favorable outcomes, including fewer rehospitalizations, better medication adherence, and greater improvement in symptoms[2,5,6].

The SMIMS project is probably the largest and most comprehensive in the world, involving multiple levels of government and disciplines. It has benefited millions of patients, including improved treatment accessibility and availability. However, some concerns have emerged over the years regarding the balance between control and treatment, the lack of an exit mechanism, and the possible restrictions on individuals once they are registered in the system.

One of the primary concerns raised about SMIMS is its perceived emphasis on control rather than treatment. Once an individual is diagnosed with one of the above six conditions, clinicians are required to report the patient's information to the SMIMS database. Once registered, patients and their families can theoretically opt out of the community follow-up, but it has been found that more than 95% of the registered cases participate in the follow-up management[2], suggesting possible pressure to enroll all registered patients.

Moreover, patients' information in SMIMS is shared with police departments and local resident committees, which has caused concerns about confidentiality and privacy. While the objective of preventing violence and crimes and ensuring social stability is important and valid, it is also important to note that individuals with severe mental illness have a much higher risk of becoming victims than perpetrators of violence[7], and control measures should not undermine the essence of patient-centered care. A reasonable balance between control and treatment is essential to avoid further stigmatizing and alienating individuals with severe mental illness, and to foster an environment where patients feel supported and empowered in their journey toward recovery[8].

The absence of an exit mechanism in SMIMS raises ethical concerns. Currently, once an individual is registered in the system, the information remains indefinitely, irrespective of whether the condition has improved, achieved remission, or was initially misdiagnosed. This practice disregards the dynamic nature of mental disorders, and the possibility of recovery or improved functioning over time. An exit mechanism would not only ensure that those who no longer meet the criteria for severe mental illness are not unnecessarily burdened, but also allow for the efficient allocation of resources to those who need them most.

The fact that the government has access to patients' information has raised concerns about patients' rights being infringed. Possible restrictions for individuals within SMIMS include denial of driver's license applications, according to the current vaguely worded regulations[9]. When patients' information is entered into the SMIMS, they are typically informed about the benefits but not the potential risks. It is not uncommon for patients and their families to question psychiatrists who made these diagnoses, leading to disputes. As a result, many psychiatrists, particularly those in outpatient settings, may hesitate to make certain diagnoses or may resort to diagnoses outside the listed six categories, such as unspecified mood disorder instead of bipolar disorder. It is worth reflecting on why a well-intentioned system has not only dissuaded many patients from participating, but has also become a source of patient-doctor conflicts.

Moreover, there is no established system to challenge or appeal the above-mentioned restrictions. Any restrictions should be carefully considered, well defined and regularly re-assessed, with a focus on protecting both the rights of individuals and the well-being of the community.

To address the challenges and improve the SMIMS, several steps are necessary. First, rigorous, independent research is needed to evaluate the effectiveness and acceptability of the system compared to historical data and parallel community-based programs. Studies need to focus on how the system impacts patients, professionals and communities. Second, the system needs to shift its focus from control to a patient-centered approach that prioritizes individual well-being, treatment and recovery. Third, SMIMS should incorporate an exit mechanism to accommodate patients who no longer meet the criteria for a severe mental illness or who have been misdiagnosed. Regular reviews of individuals' status will ensure that resources are allocated efficiently and that patients are not unnecessarily burdened by the system. Finally, any potential restrictions or limitations on individuals within SMIMS must be transparent, clearly defined, and communicated to patients and their families, and patients need to have a mechanism to challenge or appeal the restrictions.

In conclusion, we believe that the SMIMS in China represents a historically significant effort to address the challenges of managing severe mental illness within the community. However, a comprehensive, independent evaluation of the system is required, and this evaluation should inform evidence-based changes that prioritize patient-centered care, individual rights, and the overarching goal of improving the lives of patients and their communities. In particular, there is a need to address concerns regarding the balance between control and treatment, the absence of an exit mechanism, and potential restrictions on individuals' rights.

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The authors would like to thank L. Zhou for his comments on the piece.

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DOI:10.1002/wps.21212

Medication use and sickness absence from work in bipolar disorder: a nationwide register-based study

Less than half of people with bipolar disorder are employed according to population representative register-based studies from Scandinavian countries[1-3]. In those employed, maintenance of stable occupation is hindered, and sickness absences are common[4].

Antipsychotics and mood stabilizers are known to be effective in the acute treatment of mania and the prevention of relapses of bipolar disorder[5-8]. Although the medication regimen may have a considerable impact on the ability to work, the association between medication use and work attendance in people with bipolar disorder has not been addressed. The present study aimed to investigate whether the use of mood stabilizing, antipsychotic and antidepressant medications was associated with the risk of work disability, defined as sickness absence, among employed people with bipolar disorder in a nationwide cohort.

People with a diagnosis of bipolar disorder (ICD-10 codes F30 or F31, or Finnish ICD-9 codes 2962-2964 and 2967A) between 1987 and 2017 were identified from the Finnish Care Register for Health Care. The cohort included individuals aged 18 to 63 years. The follow-up started from January 1, 2005, or at first bipolar disorder diagnosis, or when people reached the age of 18 years, whichever occurred last. The follow-up ended on December 31, 2018, or when people reached the age of 63 years, or when they died, whichever occurred first.

A first-episode sample consisting of individuals with the first bipolar disorder diagnosis between 2005 and 2017 was identified from the whole cohort. Those who had used antipsychotic or mood stabilizer medications within one year before their first diagnosis were excluded from this sample.

Employment periods and sick leaves from 2005 to 2018 were obtained from the registers maintained by the Finnish Centre for Pensions and the Social Insurance Institution. The primary outcome of the study was the risk of sickness absence during employment periods. Short sick leaves (i.e., less than 10 days) were not considered.

Medication purchases were drawn from the Prescription register, and drug use periods were estimated by the PRE2DUP[9]. Antipsychotics were defined as Anatomical Therapeutic Chemical (ATC) codes belonging to N05A, excluding lithium. Mood stabilizers were lithium (N05AN01), valproate (N03AG01), lamotrigine (N03AX09) and carbamazepine (N03AF01). Antidepressants were defined as ATC codes belonging to N06A.

In statistical analysis, we utilized a within-individual design where each individual served as his/her own control. We compared medication use categories (only antidepressant, only mood stabilizer, both antidepressant and mood stabilizer, only antipsychotic, both antipsychotic and antidepressant, both mood stabilizer and antipsychotic; and concomitant mood stabilizer, antipsychotic and antidepressant) to non-use of the medications by stratified Cox regression. The time-varying covariates were the age at the start of a period, the order of medication classes, the number of prior sickness absences, benzodiazepine use (N05BA and N05CD) and Z-drug use (N05CF). Separate analyses were conducted for men and women.

The cohort included 50,072 individuals, of which 28,089 (56.1%) were women. Of the whole cohort, 22,408 (44.7%) had an employment period during the follow-up (57% women, mean age: 34.8± 11.5 years). Of the employed, 12,812 (25.6% of the whole cohort) did not have an employment period ending to sickness absence, whereas 9,596 (19.2% of the whole cohort) had such an employment period. The first-episode sample consisted of 18,000 individuals (56% women, mean age: 37.0±13.0 years), of whom 10,000 (55.5%) had an employment period during the follow-up, and 4,216 (23.4%) experienced an employment-related sickness absence.

The use of mood stabilizers, with or without concurrent antipsychotic or antidepressant use, was associated with a lower risk of sickness absence than non-use of the medications. The use of mood stabilizer only was associated with the lowest risk (hazard ratio, HR=0.79, 95% CI: 0.72-0.87), followed by the concurrent use of mood stabilizer and antipsychotic (HR=0.82, 95% CI: 0.74-0.95), and mood stabilizer and antidepressant (HR=0.88, 95% CI: 0.79-0.97). The use of antidepressant only was associated with a higher risk of sickness absence than non-use of the medications (HR=1.23, 95% CI: 1.15-1.33). Of the covariates in the analysis, the use of both benzodiazepines (HR=1.34, 95% CI: 1.24-1.46) and Z-drugs (HR=1.34, 95% CI: 1.23-1.47) was associated with an increased risk of sickness absence.

In the first-episode cohort, the results were mostly similar as in the whole cohort, but the association between antipsychotic or mood stabilizer use and sickness absence was stronger than in the whole cohort. Concomitant use of both mood stabilizer and antipsychotic was associated with the lowest rate of sickness absence (HR=0.63, 95% CI: 0.53-0.74), followed by the use of both mood stabilizer and antidepressant (HR=0.65, 95% CI: 0.54-0.79), the use of mood stabilizer only (HR=0.65, 95% CI: 0.56-0.76), and the use of antipsychotic only (HR=0.77, 95% CI: 0.66-0.90). In addition, the association between the use of antidepressant only and sickness absence was only barely statistically significant (HR=1.12, 95% CI: 1.01-1.24) (see also supplementary information).

We also examined the risk of sickness absence in women and men separately. The results were mostly similar as in the original analyses. In the first-episode sample, the risk of sickness absence when using mood stabilizer only, mood stabilizer and antidepressant, and antipsychotic only was slightly smaller, signifying stronger effect, in men than in women – e.g., for antipsychotic only, the HR was 0.66 (95% CI: 0.52-0.84) in men, and 0.86 (95% CI: 0.71-1.05) in women. Of note, the association between the use of antidepressant only and sickness absence was similar in men and women (see also supplementary information).

Thus, our study documents a notable reduction in the risk of work disability, defined as sickness absence, among individuals with first-episode bipolar disorder who were using mood stabilizers and/or antipsychotics, compared to periods without these medications. While the effect was somewhat reduced in the entire cohort, the use of mood stabilizer, either alone or in combination with antidepressant or antipsychotic, remained significantly associated with a decreased risk of sickness absence.

These results align with previous research indicating that mood stabilizers and antipsychotics are effective in the treatment of mood symptoms and in the prevention of relapses in bipolar disorder [5-8]. However, functional outcomes have been neglected in previous studies and, as far as we know, the association between work attendance and medication use has not been investigated previously. The results of this study underscore the importance of effective treatment especially in early stages. Treatment may also be able to reduce the secondary effects of the illness, which hinder the ability to pursue and sustain employment. On the other hand, the use of antidepressant medication only was associated with an elevated risk of sickness absence. Although this finding may be in part due to confounding by indication (depressive symptoms are known to be strongly associated with reduced work attendance), it nonetheless highlights the need for more effective medication options to manage depressive episodes in people with bipolar disorder.

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This study was funded by the Academy of Finland (grant no. 310295). Supplementary information on the study is available at https://osf.io/8kx7v/?view_only.

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DOI:10.1002/wps.21213

Modulating self-referential processing through meditation and psychedelics: is scientific investigation of self-transcendence clinically relevant?

Self-referential processing is a core feature of human experience and includes a variety of mental faculties that support conception of the self, including internal representations that associate salient information to one's identity. It is well understood that self-referential processing is important for the onset, maintenance, prevention and treatment of psychiatric conditions, including mood, anxiety and substance use disorders. Here we propose that meditation and psychedelics may modulate self-referential processing by inducing self-transcendence, and call for further research on this transdiagnostic mechanism of action.

Meditation and psychedelics have gained renewed traction in psychiatry after initial interest in the 1970s. Meditation is a form of cognitive training with the goal of improving attentional and emotional self-regulation and inducing self-transcendence. Psychedelics are powerful psychoactive substances that alter perception and mood; affect numerous cognitive processes, including the sense of self; and have been preliminarily shown to have therapeutic effects in mood and anxiety disorders.

It can be argued that meditation science has undergone two epochs, and that we are currently entering a third. The first epoch, which occurred approximately between 1995 and 2005, was characterized by two types of studies. The first set of studies provided initial, and then replicated, results indicating therapeutic effects of meditation across many domains (e.g., depression, anxiety and pain), with variable effect sizes. A concurrent second set of studies provided initial investigation of differences between experienced meditators and novices, focusing on heretofore unexplored effects of meditation on the brain. The second epoch, roughly 2005-2020, was characterized by increasingly rigorous, full-scale randomized controlled trials (RCTs) and mechanistic research to elucidate cognitive-affective mechanisms that might underlie meditation's health-related benefits. For example, researchers used functional neuroimaging to investigate attention and emotion regulation, and the relations of these processes to health and well-being, including psychiatric outcomes.

We suggest that meditation research is entering now a third phase, moving beyond the focus on its attention and emotion regulatory mechanisms, and toward the study of advanced meditation, that is, states and stages of practice that unfold with increasing mastery, including more profound psychological transformations, such as self-transcendence and non-dual awareness (i.e., the experiential unification of the subject-object dichotomy that normally structures human experience). The clinical outcomes and neural mechanisms of such self-transcendent experiences have now begun to be studied in the context of psychedelic-assisted psychotherapy.

To date, the effect of meditation has been predominantly explored through a lens of stress reduction. For example, mindfulness-based stress reduction, the best known and most widely applied manualized intervention based on meditation, was designed to reduce participants' stress, although it was later found to be effective also in reducing anxiety and depression symptom severity in a broad range of individuals. We are now on the cusp of a new wave of research and clinical applications that instead focus on aspects of advanced meditation, including self-transcendence.

Self-transcendence – characterized by ego dissolution, affective bliss, and a merging or softening of boundary between self and other/object (i.e., non-duality) – is a phenomenological experience reported across multiple contemplative, philosophical, religious and spiritual traditions around the world for thousands of years. This experience is valued as a catalyst for compassionate behavior and self-actualization. Considerable evidence indicates that psychedelics can induce radical experiences of self-transcendence. We argue that self-transcendence, and what have been called altered states of consciousness or peak experiences, should be a legitimate area of study. We believe that it is now warranted to rigorously interrogate these phenomena in the context of modern psychiatry, and that this pursuit may provide new avenues to foster psychological thriving in clinical and non-clinical contexts.

In a RCT (N=165), we recently found that a mindfulness-based intervention for opioid misuse elicited self-transcendent experiences marked by ego dissolution, bliss, and non-dual awareness to a significantly greater extent than an active psychotherapy control[1]. Self-transcendent experiences were associated with increased frontal midline theta EEG power during meditation, which mediated effects of mindfulness-based intervention on decreasing opioid misuse through a 9-month follow-up. These effects were robustly replicated in another study[2]. Two other recent RCTs have shown that developing increased self-transcendence through meditation is associated with decreases in chronic pain[3,4].

Psychedelics have also been linked to self-transcendence in clinical trials[5], and some neuroimaging studies have identified associations between self-transcendence (sometimes called ego-dissolution in the psychedelic literature) and deactivation of the default mode network[6] and activation of cortico-striato-thalamo-cortical circuitry[7].

The study of self-transcendence, and other aspects of advanced meditation, will benefit from a more nuanced understanding and testing of the phenomenology of these experiences, the kinds of practices that lead to them, and their developmental trajectories (meditative development) and outcomes (meditative endpoints). Neuroimaging studies of self-transcendence and advanced meditation more broadly (e.g., related to altered perception of time, space and reward-related processes) could provide mechanistic understanding to inform computational models of modulating aberrant neural systems (e.g., dysfunctional self-referential processes implicated in psychiatric disorders and modulated by meditation and psychedelics[8]).

Ultimately, this line of research has the potential to stimulate the development of novel treatments for psychiatric illness, including combination therapies that integrate existing mindfulness-based interventions and psychedelics, novel meditation-based therapies grounded in contemplative traditions and practices not yet extensively studied by Western science[9], and novel neuromodulation protocols to target neural networks with neurofeedback and brain stimulation.

Self-transcendent experiences may prove to be a means of restructuring the neural system dysfunction that underlines the development and maintenance of a range of maladaptive behaviors and mental states. By pursuing this scientific frontier to deeply understand advanced meditation, including meditative development and endpoints, and psychedelic-assisted psychotherapy, we may access a great and untapped potential to alleviate suffering and advance human flourishing.

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M.D. Sacchet is supported by the National Institute of Mental Health (R01MH125850), the Dimension Giving Fund, and the Brain and Behavior Research Foundation (grant no. 28972). E.L. Garland is supported by the National Center for Complementary and Integrative Health (R01AT011772) and the National Institute on Drug Abuse (R01DA056537, R01DA057631, R01DA048094).

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DOI:10.1002/wps.21214

Clinical translation of expert-endorsed cognitive rehabilitation interventions for substance use disorders

In a recent Delphi consensus[1], we endorsed the application of four cognitive rehabilitation interventions as adjuncts to the treatment of substance use disorders: cognitive bias modification, contingency management, cognitive remediation, and emotion regulation training. This innovative portfolio is poised to cover the unaddressed need of tackling cognitive alterations that can hinder the efficacy of current treatments for substance use disorders[2]. Here, we summarize the therapeutic mechanisms of these four interventions, discuss barriers to their translation into clinical practice, and provide recommendations on how to overcome these barriers.

Cognitive bias modification is a family of interventions that aim to reset drug-related biases using different varieties of computerized cognitive training. One example redirects tendencies to approach the drug toward alternative targets (e.g., from a tendency to approach alcohol to a tendency to approach a non-alcoholic drink). Contingency management provides tangible incentives (e.g., monetary payments) in exchange for therapeutic goal achievement (e.g., treatment attendance, abstaining or reducing drug use). Both cognitive bias modification and contingency management target addiction-related alterations in the incentive salience system by reducing the value of drug rewards and increasing the value of alternative reinforcers[3].

Cognitive remediation trains mental strategies aimed to restore or circumvent cognitive deficits, with a view to improving everyday function. For example, a "pause – check your goal – choose" strategy can be used to thwart impulsive choices within high-risk scenarios such as social engagements (especially those involving people who use drugs) or family gatherings, which can be highly confrontational for people in recovery. Emotion regulation training also uses a variety of mental strategies, in this case focused on improving management of negative emotions (e.g., cognitive reappraisal) and enhancing positive affect (e.g., savouring of natural reinforcers). Both cognitive remediation and emotion regulation interventions target addiction-related alterations in the executive control system by strengthening top-down control of behavior and emotions[3].

The Delphi experts recommended applying these interventions after acute detoxification, and maintaining them weekly for at least three months. The selection of the specific intervention/s should be based on individualized neuropsychosocial assessments, with the caveat that some interventions are best suited for particular substance use disorders (e.g., cognitive bias modification for alcohol use disorder). Different interventions can be combined to enhance treatment efficacy, as shown for the combination of cognitive remediation and contingency management[4].

Although the four expert-endorsed interventions are evidence-informed, multiple factors hamper their translation into clinical practice. These factors include the controversies around the concept of addiction, the divide between the research and clinical worlds, the lack of availability of technology and other resources, and the intricate policy landscape.

Cognitive rehabilitation interventions are anchored in neuroscience evidence, but this approach is at risk of being equated with reductionist "brain disease" models of addiction, which have been criticized for neglecting the social aspects of the disorder and their limited contribution to help-seeking and treatment[5]. This may create a tension between the scientists and practitioners within the social and behavioral treatment space and the proponents of neuroscience-based approaches.

An additional gap exists between the research community that develops cognitive rehabilitation interventions and those who train the treatment workforce that could implement them. These groups have different forums and priorities, also underpinned by disparate institutional incentive structures and performance indicators. To compound this problem further, there are limited opportunities to train addiction clinicians on neuroscience principles and approaches[6].

Cognitive rehabilitation interventions also require specific technology and material resources, such as computers and cloud-based services, and dedicated budgets for incentives, which may be prohibitive for mainstream treatment services. The broader policy and service provision landscape may pose additional challenges by opposing resistance (e.g., to contingency management) or lacking resources and/or agility to integrate these novel approaches within accessible, government-supported treatment plans.

Notwithstanding these barriers, progress in scientific collaboration practices and translational science now provide a novel springboard to enable integration of cognitive rehabilitation in addiction clinical care.

We previously referred to the "tension" between the behavioral/social and neuroscience approaches, but we argue that this tension is artificial, because cognitive rehabilitation interventions: a) leverage both neuroplasticity and learning principles to promote not only brain health but also adaptive changes in behavior and social function; b) should be understood and applied as add-ons rather than replacements for existing treatments. This integrative view is aligned with recent recommendations from the World Health Organization to nurture brain health in the context of its manifold individual and social determinants[7], and relates back to the bio-psycho-social model of addiction. As many other psychiatric disorders, substance use disorders require a complexity-based approach that aims to optimize brain health by creating feedback loops with community resources and environmental mechanisms[8].

The more pragmatic gap between research and clinical worlds can be tackled with effective approaches derived from translational science, such as co-location and co-production. Co-location can start as early as during graduate clinical training, in masters and doctoral level programs, in which students can act as translators of research knowledge to become early-adopter clinicians. Co-production – which involves partnerships between researchers, clinicians and service providers towards the design of specific treatment solutions – provides unique opportunities for engagement of the addiction treatment workforce. It allows, for example, to develop case examples that are tailored to the individual and contextual needs, as well as delivery modalities and business models that are suitable and feasible. Furthermore, collaboration with industry partners can be leveraged to develop health technology solutions to optimize the user experience and engagement with interventions.

Co-location and co-production also enable multiple opportunities for shared discussion forums among researchers, clinicians and decision-makers, which can facilitate coalescence of indicators of success across the research and clinical worlds (e.g., greater emphasis on translational outcomes for researchers, and greater opportunities for clinicians to participate in research). Moreover, changes in incentive structures can increase capacity and motivation for neuroscience training within the addiction treatment workforce, which can be expedited using e-learning and train-the-trainer approaches.

Support from funding bodies is critical to bridge the technology and resources gap. Over $1.4 billion per annum is currently spent in addiction research only in the US; however, it has been estimated that only 15% of funded medical research is eventually translated into clinical practice[9]. It makes both good financial and public health sense to devote a significant proportion of that funding to enable service providers to catch up with evidence-based interventions. Specific funding schemes for non-governmental organizations and not-for-profit institutions to acquire the technology and resources needed for implementation of cognitive rehabilitation interventions would be a practical solution to reduce the current translation gap.

These novel technologies and resources could also be used to monitor the outcomes of cognitive rehabilitation delivery in real-world clinical settings, as well as to analyze its impact on value-based health outcomes directly informed by consumers. In so doing, we envision a future in which cognitive rehabilitation is embedded in standard treatment pathways to maximize the health and well-being of individuals with addiction.

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DOI:10.1002/wps.21126

Achieving equality, inclusiveness, and cultural sensitivity in mental health (EDIT)

In this era marked by unprecedented global challenges, mental health remains a key issue affecting individuals across diverse ages, cultures and backgrounds. According to the latest World Mental Health Report[1], 970 million people (13% of the global population) live with a mental health disorder, including 248 million youth.

Though high-income countries exhibit a slightly higher prevalence of mental disorders (15.1%) relative to low-income countries (11.6%), more than four out of five individuals with a mental disorder (82%) live in low- and middle-income countries (LMICs), due to their larger population size.

Historically, mental health care has been marked by disparities, with certain populations facing stigma, discrimination, and limited access to services. Compared to the general population, ethnic and sexual minorities are often more likely to be affected by mental disorders, but less likely to use mental health services[2]. Gender inequalities also exist, and are often driven by societal expectations and cultural norms. While depressive and anxiety disorders are more prevalent among women, men are more prone to substance use disorders[3]. Societal pressure related to body image, unequal workplace opportunities, and gender violence exposes women to higher risk of eating disorders, occupational stress, and trauma-related disorders. On the other hand, men may face more barriers in accessing mental health treatment due to societal pressures that discourage them from seeking help.

Across the world, mental disorders are a leading cause of disability, exerting a huge impact on individuals' and families' daily life and functioning. The life expectancy for people with severe mental disorders is drastically reduced[4]. Nevertheless, only 2% of global health expenditures are allocated to mental health. Indeed, the treatment gap for mental disorders is above 50% in all countries in the world, and can reach 80-90% in LMICs[5].

Societal attitudes toward mental health can foster stigma and discrimination that in turn prevent individuals from seeking help. Help-seeking can also be discouraged by a lack of awareness of the signs and symptoms of mental disorders and of available effective treatments, by cultural beliefs and practices, by language barriers, and, ultimately, by personal barriers, such as fear of treatment and stigma superimposed on insufficient motivation[6].

People with mental disorders are more likely to experience various forms of social and health inequality. Unemployment is high in this population[7], resulting in financial and housing insecurity. Unhealthy behaviors – such as excessive alcohol consumption, smoking, poor nutrition and sleep, and sedentariness – are also common among people with mental disorders and expose them to a higher risk of physical diseases[8].

Considering these socioeconomic and cultural implications, the WPA Action Plan 2023-2026[9-11] advocates for a more comprehensive and inclusive approach to mental health.

In order to reaffirm the WPA's commitment to promoting good mental health and well-being for all individuals and communities around the world, the Action Plan introduced the EDIT initiative.

The EDIT acronym stands for:

- *Equality across genders, ages and ethnicities*. The WPA aims to ensure that mental health care is accessible to all, by reducing disparities based on factors such as ethnicity, age, gender, sexual orientation, geographical location, and socio-economic status. By promoting research, education, and policy changes, the WPA seeks to create a world where mental health is a universal right. At the same time, the WPA emphasizes the need for a culturally competent psychiatry able to recognize and address the unique challenges faced by different populations and communities.
- *Developmental stages from childhood to adulthood and beyond*. The WPA recognizes the dynamic nature of mental health, which changes across the lifespan, and therefore encourages a life-course approach to health and mental health[12]. There is a need to train psychiatrists specialized in dealing with the unique manifestations of mental disorders at different stages of life. Furthermore, since about 40% of mental disorders are established by the age of 14 years, early prevention and interventions should be prioritized[13].
- *Inclusion of under-represented groups*. The WPA is committed to foster diversity and inclusivity in all its activities. The viewpoint of marginalized groups and people with lived experience should be considered in every phase, from research to clinical treatment.
- *Transcultural awareness and perspectives*. As cultural belief systems, values and practices shape the clinical expression and personal experience of mental disorders, the research questions and the provision of mental health care in contemporary multicultural societies pose enormous challenges. The WPA underscores the need for culturally sensitive approaches that acknowledge and respect this diversity. This involves not only understanding the cultural context of mental health, but also adapting research questions and treatment approaches to be culturally sensitive. In this sense, the WPA aims to foster collaboration between researchers and mental health professionals from different cultural backgrounds to expand the breadth and depth of knowledge, and promote a culture of understanding, acceptance and trust.

To achieve these goals, effective communication plays a fundamental role. By enhancing dialogue and promoting mental health literacy and awareness, the WPA aims to destigmatize mental health issues and create a more open and understanding society. The WPA recognizes the need for improved communication not only within the psychiatric community, but also with stakeholders, people with lived experiences, and the general public. To meet this need, several new communication initiatives are encouraged, harnessing the great potential of digital technologies.

One platform under creation, called the Specialist Corner, is aimed at updating clinicians about the latest findings and enabling them to discern and adopt best practices. The platform will consist of a series of short, easily-digestible webinars on major mental disorders, covering the state-of-the-art treatments and best practices for daily psychiatric work, including aetiology, symptoms, comorbidities with physical diseases, and rehabilitation strategies from the gender, developmental stage, and cultural perspectives. Moreover, follow-up webinars will feature prevention, healthy lifestyles, caregiver and family, digital psychiatry, and human rights/ethics perspectives from experts in these fields. Reader-friendly educational materials from the webinars will be developed for patients, their families, clinical staff, and the general public.

Another platform on the WPA website, the Healthy Lifestyles Hub, is a library of resources accessible to psychiatrists worldwide, with the purpose of demonstrating how mental health can be improved through the adoption of healthy lifestyles. Videos on physical activity and good nutrition have been developed for easy use in clinical practice. Furthermore, engaging both patients and psychiatric staff in joint sessions of physical activity will strengthen connections, cohesion and collaboration, improve mutual understanding, and reduce hierarchical divisions.

Without breaking the language barriers, however, it will be impossible to ensure the accessibility of these resources to psychiatrists worldwide. For this reason, the WPA is committed to making the materials available in as many local languages as possible, through the engagement of Member Societies and of young, enthusiastic psychiatrists.

In conclusion, the WPA Action Plan 2023-2026 acknowledges the interplays between all aspects of human experience and mental health, and aspires to address the diverse needs of individuals across the lifespan and from various cultural backgrounds. The WPA continuously tries to strengthen ties with other international organizations in the fields of psychiatry, neurology, and public mental health, including service users and family carers organizations.

Through collaborative efforts in research, education, clinical practice, advocacy, and policy changes, according to the United Nations Sustainable Development Goals, the WPA seeks to shape a world where actions to improve mental health are universally accessible, culturally sensitive, and inclusive[13].

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DOI:10.1002/wps.21220

Being a strong voice for mental health parity, human rights, and community-based psychiatric care in challenging times: developing the WPA Action Plan 2026-2029

The last decade has borne witness to WPA's steadfast and unwavering commitment to advancing psychiatry in every corner of the world. Demonstrating a great deal of professional resilience, all bodies of the WPA have delivered on this promise despite an ever more challenging global political landscape, natural disasters, massive refugee crises, the COVID-19 pandemic, and economic downturns.

The previous Action Plans of the triennia 2017-2020[1] and 2020-2023[2,3], as well as the current one (2023-2026)[4,5], have skillfully and effectively addressed these challenges by developing programs geared towards people living in adversity, suffering from long-standing illnesses and psychosocial disabilities; by closely working with people with lived experience and their caregivers; by emphasizing sustainable developments as a prerequisite for total health; by supporting psychiatrists in their roles as policy makers, service providers, as well as trainers and supporters of health care workers; and finally, by implementing evidence-based therapies, prevention, and adoption of healthy lifestyles.

Over the past six years, the WPA has implemented measures to swiftly communicate with its various bodies and tailor these initiatives to both the demands and opportunities of the 21st century. Guided by the principles of diversity, equity and inclusion, the WPA has created resources to further activities for early career psychiatrists, focusing on colleagues in low- and middle-income countries[6]. WPA's activities, which are enriched by the active participation of patients and caregivers, are also supported by large publicly funded grants, boosting the educational and scientific mission of the association[7,8].

It is against this backdrop that I am planning to build on and continue the core mission of the previous Actions Plans, i.e., consolidating psychiatry as an integral and indispensable part of medicine serving the most vulnerable around the globe. While triennial Action Plans may differ at the level of specific programs, I firmly believe that, in an ever more distressing world, the WPA must develop and promote a core set of goals.

Looking back at my work with the WPA during the past decade, I would posit that three core goals have emerged: a) working towards mental health parity in all imaginable areas and at all levels; b) championing human rights as a moral foundation of our discipline; and c) building strong and lasting community-based psychiatric care. While one can formulate many more goals, I believe that these three aims capture the essence of what the WPA considers its paramount mission: advance psychiatry and mental health for people all over the world.

Mental health parity has been a buzzword for many years[9,10]. However, it is more than that. It is a constant reminder that our field must fight for the needs and rights of our patients, their families and caregivers, our colleagues, and institutions around the globe and around the clock. This leads us to the second goal: standing up for mental health parity means fighting for human rights. It is my goal that universal human rights guide WPA's activities and policies: wherever mental health and mental health care are threatened, through lack of education or hurtful policies; through unwarranted cuts to resources; through ethnic or religious persecution, or genocide[11]; or through threats to livelihoods due to natural disasters and climate change[12], the WPA needs to be the voice to call for decisive action, creating and defending environments full of diversity and equity. Also, it is my sincere belief that we are called to action whenever and wherever psychiatry is abused by rogue political actors to suppress universal freedoms.

Finally, all these actions need to start within the community. Working with all stakeholders, we need to reach out to where our expertise is needed, building sustainable and trust-based networks of care and education[13]. I will make sure that this outreach will be in lockstep with our Member Societies, whose ideas and input will be crucial for the success of this mission. To this end, we will also have to develop close partnerships with other organizations, while always being true to what we are: a medical discipline deeply rooted in science and guided by empathy towards those who seek our help.

Developing a roadmap for these goals is not an easy task and needs many hands and minds. To this end, I am very grateful that I will be joined by a diverse group of highly esteemed colleagues from around the world who will be part of the 2023-2026 Standing Committee on Planning. They are (in alphabetical order): R.S. Abdelazim (Egypt), R.N. Córdoba Rojas (Colombia), M.Á. Cuéllar Hoppe (Paraguay), P. Falkai (Germany), C. Jatchavala (Thailand), M. Mimura (Japan), B. Oladeji (Nigeria), P.S. Sachdev (Australia), G. Saha (India), and L. Yatham (Canada). These renowned colleagues do not only represent a large part of WPA's regions, but hail from various sub-specialities of our discipline. They are educators, clinicians and/or researchers; leaders of national or international professional societies; or proponents of the WPA's Early Career Psychiatrists program.

Working with all bodies of the WPA, the members of this Committee will support, advocate for, and continuously evaluate existing initiatives that have proven successful. Moving forward, they will support the President-Elect and the current Executive Committee in strengthening the WPA's leading global role in state-of-the-art, evidence-based, and empathy-driven global public mental health care, psychiatric practice, research, and education.

Thomas G. Schulze
WPA President-Elect

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DOI:10.1002/wps.21215

The blueprint for advancing psychiatric education and scientific publications

Income inequality, wars, increasing numbers of refugees, pandemics and climate change are but a few of the many, compelling challenges that we are facing today. All people and all countries are affected, with the most vulnerable, especially our patients, suffering disproportionately. The recent crises have also raised awareness about the importance of mental health, but the growing need for care has simultaneously increased demands on the already limited and overwhelmed mental health service systems.

It is in this environment that we see a demand for the WPA to energetically support solutions to these challenges, also by advancing its educational and publication agenda, while taking other actions necessary to ensure the sustainability of its efforts and the universal availability of its products in support of service providers around the world.

For the first time, the WPA has consolidated the coordination of its educational and publication activities under a single Secretary. This initiative involves establishing a single Standing Committee on Education and Scientific Publications. This Committee will oversee the development of the WPA educational programs and the preparation of materials for these programs. It will also be responsible for the implementation of WPA continuing medical education accreditation. In addition, it will oversee the development of the WPA publication policies, while also facilitating the preparation and distribution of materials for publication.

The WPA Committee on Education and Scientific Publications is committed to and enthusiastic about engaging WPA Member Societies, with the hope that they will join in this transformative journey. Within this context, the Committee invites all the WPA components to actively contribute to and support the following objectives: a) the Association will expand its educational and publication activities to support its Member Societies as they strive to meet the ever-increasing demand for mental health services; b) the Association will be innovative, dynamic and inclusive, while it places emphasis on sustainable education and scientific publications; c) the Association will enhance its global presence in the area of education and publications by leading inter-agency collaborations in support of psychiatrists and psychiatry, by attracting the brightest young people to psychiatry, and by providing the relevant services necessary to encourage and sustain WPA membership.

Scientific publications play a crucial role in advancing knowledge and skills, with the ultimate goal of improving patient outcomes and enhancing mental health on a global scale. Over the years, the WPA has endeavored to achieve these goals through its publications, including but not limited to journals, conference proceedings, and books.

World Psychiatry is the flagship journal of the WPA. As WPA President (1999-2002), Prof. J.J. López-Ibor stated: "*World Psychiatry* mirrors the best of our psychiatrists and the WPA: encompassing hopes, opportunities, commitment to science and ethics, dedication to patients and society, and the courage to foster growth"[1]. Our Committee looks forward to supporting Prof. Mario Maj, the Editor of *World Psychiatry*, to ensure the continuing success of the Journal.

It is now timely to examine the roles of journals affiliated with the WPA. Ironically, official information is not readily available in this respect. However, unofficial sources identify some 14 scientific journals with a stated connection to the WPA or one of its Scientific Sections. However, even the most cursory examination suggests that some of these journals currently have limited connections to the WPA. In order to more thoroughly clarify this situation, the Committee will collaborate with A. Soghoyan, WPA Secretary for Scientific Sections, and the relevant Standing Committee, to assess each of these journals with respect to their relationship to the WPA and its mission. Upon completion of this exercise, the WPA Committee on Education and Scientific Publications will offer assistance to those journals that require and want support.

We have received inquiries from WPA zonal and regional leaders regarding the possibility of establishing local psychiatric journals. The WPA Committee on Education and Scientific Publications will provide support and guidance to colleagues pursuing these efforts, as is appropriate and necessary.

The WPA also collaborates with various journals which have no formal links with the Association, including facilitating special issues. The WPA Committee on Education and Scientific Publications will facilitate collaboration with other journals, including special issues, ensuring high quality of papers. We will engage with journals in mental health and psychiatry, as well as with leading medical journals, in an attempt to facilitate featuring psychiatrically relevant topics. This commitment extends beyond journals, supporting WPA Scientific Sections as they endeavor to publish books and other materials, including those for online delivery as texts or in other formats[2,3].

Finally, the Committee on Education and Scientific Publications will launch an e-journal/newsletter to disseminate information regarding its activities to all WPA components.

The COVID-19 pandemic has been a catalyst for the WPA to hasten development and promotion of an online Education Portal, aiming to promote dissemination of mental health knowledge and skills worldwide[4,5]. As of January 2024, the Portal registers 2,772 users from 119 countries, utilizing 18 languages and accessing 94 resources. Later in 2024, the current educational platform will be closed, and materials will migrate to a new, more effective and efficient learning center.

While recruiting to psychiatry has been an ongoing challenge, the increasing recognition of the importance of mental health, and the need to reduce stigma, has resulted in several creative and effective national recruitment strategies. The WPA, together with Member Societies, will analyze these experiences and identify methods to adapt and implement them across the world. While prioritizing training and support to its membership, the WPA will also focus on innovative educational programs aimed at preventing burnout and other forms of professional distress.

Many individuals have significantly contributed to their national society and/or the WPA. Such expertise should not be lost prematurely through retirement or semi-retirement. The WPA shall identify opportunities for psychiatrists who, even after retirement, wish to remain involved in programs that match their expertise and are important to global training needs around the world. For example, by forging a strong partnership with the WPA Workgroup on Volunteering[6], the Committee on Education and Scientific Publications will streamline and optimize the coordination of activities related to education and scientific publications. This collaboration will involve regular communication, joint planning sessions, and shared resources to ensure a cohesive and effective approach to achieving common goals.

The emphasis on education is central to the WPA Action Plan 2023-2026[7-9]. The Committee on Education and Scientific Publications is dedicated to supporting this effort and determined to provide the very best in educational and scientific materials to our WPA colleagues and all professionals working hard to improve the mental health of our communities around the world.

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DOI:10.1002/wps.21216

Report from the WPA Secretary for Scientific Sections

WPA Scientific Sections are established and discontinued by the General Assembly on the proposal of the Executive Committee[1]. There were 55 Scientific Sections in 2004, 65 in 2006, 68 in 2013. Currently there are 66 Scientific Sections and four Special Interest Groups. Their coordination is under the responsibility of the Secretary for Scientific Sections[2].

The aims of WPA Scientific Sections are the collection, analysis, presentation and dissemination of information concerning services, research and training in the various fields of psychiatry and mental health, and the advancement of scientific knowledge in these fields.

Special Interest Groups provide a forum on key issues within psychiatry and mental health. They include experts and interested professionals in their respective areas. Their main objective is to encourage the WPA membership to work in areas that at a later stage may require the establishment of a Scientific Section[1].

The two previous Secretaries for Sections, A. Javed and T. Schulze, have done a tremendous work, which is partly reflected in many developments which have occurred during the past triennium[3-13].

Several information technology advances have been put in place to give the Sections a corporate identity and to allow them to work more efficiently. A system has been created whereby Sections can now update their website using a personalized link. The Sections are also provided with a web-based form to submit their triennial activity report to the Secretary for Sections, needed for their reinstatement[2].

The past triennium has seen the roll-out of the Education, Science, Publication and Research Initiative (ESPRI), a vehicle to jumpstart research projects in low- and middle-income countries, with the WPA providing seed funding to (preferably) early career investigators to carry out scientific projects of relevance to their respective country or region, and for which funding would be difficult to obtain otherwise[6].

The ESPRI was initially conceptualized by the Secretary for Sections, co-developed with the Secretaries for Publications and Education, and approved by the Executive Committee. To date, the WPA has funded six projects from around the globe, addressing a variety of issues: major depression in old age (Tanzania); psychological impact of Ebola and COVID-19 infections (Liberia); genomics of bipolar disorder (Nigeria); poverty alleviation for persons with mental health problems (Pakistan); transdiagnostic and transcultural web-based psychotherapeutic tools (Pakistan); training tools for the examination and documentation of the psychological sequelae of torture and war (UK, Austria and Syria).

There has been a major uptick in WPA's direct research involvement, as the Association has been awarded principal investigator status in two large European Union Horizon research grants, with the Secretary for Sections taking the lead in the grant submission process, aided by the Section on Genetics in Psychiatry[6]. The WPA currently has principal investigator status in the PSY-PGx Consortium, focusing on the implementation of pharmacogenetics in psychiatry, aimed at the identification of biological and clinical markers predicting resistance to pharmacological treatment approaches. This research work will be jointly coordinated by the Executive Committee and will involve several Scientific Sections. The WPA will work closely with the Global Alliance of Mental Illness Advocacy Networks (GAMIAN) Europe, a not-for-profit patient-driven pan-European organization, hence further developing its mission of promoting "trialogue"[6].

Currently there are well-established and dynamic mechanisms underlying the work of WPA Scientific Sections. However, we have very active Sections that are doing more than international associations in their field, while there are other Sections which need to be revitalized to meet the basic requirements indicated in the WPA by-laws. We will have to create the conditions for the best functioning of each Section, and this will require a joint action by the Executive Committee, under the guidance of the WPA President, the Council, and the leaders and members of all the Sections.

All the planned activities will have to be in line with the WPA Action Plan 2023-2026[14-16], approved by the General Assembly at the Vienna World Congress. Collaborations with international professional associations in the fields of psychiatry, neurology and public mental health, as well as partnerships with representatives of service users and organizations of family carers, will have to be continued and intensified.

The WPA aims to contribute to the achievement of the third United Nations (UN) Sustainable Development Goal ("Ensure healthy lives and promote well-being for all at all ages"), and the work of Scientific Sections will be crucial in this respect. This will require a cooperation with a variety of partners, also beyond the fields of public health, targeting areas such as climate action, labour, housing and education.

Promotion of healthy lifestyles and suicide prevention at the population level, and enhancement of the mental and physical well-being among psychiatric patients and staff, are major priorities highlighted in the WPA Action Plan 2023-2026[14-16], and will be a main component of the activity of many WPA Scientific Sections.

The collaboration among the various Scientific Sections, and between these Sections and Special Interest Groups, in research and training activities will be actively pursued during the next triennium, mostly but not only as part of WPA scientific meetings and educational products.

In this rapidly changing world, those organizations will survive and benefit which will not only follow their traditional principles, but also create new flexible mechanisms to implement their mission, which in our case is to provide highly ranked services to patients, families and the entire community; to ensure the professional development of psychiatrists and other mental health workers; and to contribute to the promotion of mental and physical health at the population level. This will require a very hard collaborative work, to which all of us are prepared.

Armen Soghoyan
WPA Secretary for Scientific Sections

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DOI:10.1002/wps.21217

Report by the WPA Working Group on Developing Partnerships with Service Users and Family Carers (2020-2023)

All 187 ratifications of the United Nations Convention on the Rights of Persons with Disabilities[1] come along with legal obligations along the lines of "Nothing about us without us!", a long-standing demand of the organizations that represent hundreds of millions of persons with disabilities around the globe.

In a historic first, in the early years of this century, mental health-related conditions became recognized as part of the broader disability sector and, within this context, referred to as psychosocial disabilities. This allowed for persons with mental health conditions to feature prominently in global disability-related advocacy initiatives to promote and protect human rights of all persons with disabilities.

In another historic first, self-advocates were an essential part of the negotiating and drafting process of the Convention. The first human rights treaty of the 21st century was the product of a truly participatory process. No policy development, review and amendment of legislation or additions to regulations shall be undertaken without including experts in their own right, namely persons with psychosocial disabilities.

The international consensus on working in partnership is in the process of turning into reality around the globe. According to the 2020 World Health Organization (WHO)'s Mental Health Atlas[2], 35% of the 171 countries that responded to the survey reported ongoing formal collaboration with service users and/or family/caregiver advocacy groups.

Professional psychiatric organizations have a significant role to play in creating opportunities for meaningful, authentic and sustainable involvement of persons living with a psychosocial disability in their work.

At the international level, examples are the World Association of Psychosocial Rehabilitation, which includes persons with lived experience of mental health conditions and family carers as board members; the European Psychiatric Association, which includes ex-officio members of the boards of the European Federation of Associations of Families of People with Mental Illness (EUFAMI) and the Global Alliance of Mental Illness Advocacy Networks (GAMIAN); and the Collaboration Agreement between Mental Health Europe (MHE) and the European Network of (Ex-) Users and Survivors of Psychiatry (ENUSP).

At the national level, examples are the Royal Australian and New Zealand College of Psychiatrists with its Community Collaboration Committee, whose members contribute to the training, assessment and accreditation of psychiatrists, as well as to mental health policy direction and internal operations of the College; and the UK Royal College of Psychiatrists, with a family carer and a user representative as council members.

Some government bodies also have persons with lived experience background on board. A prominent example is the Advisory Committee on Mental Health set up by the Hong Kong SAR Government. With the advice and support of this Committee, the Hospital Authority of Hong Kong has ensured that every mental health service cluster recruits a specified minimum number of trained peer expert workers in its mental health teams for people with serious mental health problems. Another example is the National Mental Health Commission of the Australian Government.

Examples of international policy and research endeavors with partnerships are the Lancet Commission on Mental Health, Stigma and Discrimination[3], which included people with lived experience background in key leadership roles; and the WHO QualityRights initiative[4], which has taken multipronged actions to put people with lived experience at the centre of its global and country level work to transform policy, law and services, and to build capacity on person-centred and rights-based approaches to mental health.

The Global Mental Health Peer Network has developed formal partnerships with several international organizations, including the International Initiative for Mental Health Leadership, Ember Mental Health, and Recovery IPSS. These partnerships are aligned with its "Considerations when working and engaging with persons with lived experience of mental health conditions". Rules of engagement for successful partnerships include principles of transparency and fairness, ways of finding a common language, making decisions by consensus or democratically, and moving from tokenistic participation to active and engaged partnerships[5].

Examples of training partnerships include the US National Association of Mental Illness (NAMI)'s in-service training for mental health professionals, provided by a team consisting of an adult with a mental health condition, a family member and a mental health professional who is also a family member or has a mental health condition; the Fundación Mundo Bipolar's trainings developed within the project RECOVER-E; and the EUFAMI's training programme "Prospect for People".

For more than three decades, the Trialogue experience of learning and practicing communication on equal footing has been providing a discrete and independent acquisition and production of knowledge for people with a lived experience of mental health problems, family members and friends, as well as persons working in the mental health field[6].

The WPA has been working towards inclusion of service users and family carers in all aspects of mental health for many years. Its "Recommendations on Best Practices in Working with Service Users and Family Carers"[7] resonate in its Madrid Declaration. The momentum was revived with the creation of the Advisory Group for Service Users and Family Carers and their work in the triennium 2017-2020. This work was continued by the Working Group on Developing Partnerships with Service Users and Family Carers, established as part of the WPA Action Plan 2020-2023[8-10].

This Working Group has cooperated with many WPA components and has been involved in all World Congresses during the triennium, organizing symposia on a variety of topics, ranging from somatic health of persons with mental health conditions to human rights and mental health, as well as courses on alternatives to coercion in mental health care. The latter have been the outcome of a fruitful cooperation with the WPA Working Group on Implementing Alternatives to Coercion in Mental Health Care. This partnership included research, education, and co-authorship of a position and other academic papers. A cooperation was also implemented with the WPA Working Group on Volunteering[11].

The Working Group also organized in 2023 two WPA webinars on "There's no mental health care without human rights" and on "The why and how of successful partnerships between psychiatrists and service user and family/carer advocacy movements".

Finally, the Working Group produced a Position Paper on "Developing Partnerships with Service Users and Family Carers", which was adopted by the WPA General Assembly in September 2023. This Position Paper recommends that "all international and local professional organizations, including WPA programs and member societies, find appropriate ways to work in authentic and meaningful partnerships with persons and/or organizations with personal experience of mental health conditions as well as with family and informal carers".

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DOI:10.1002/wps.21221

Acknowledgement
This publication has been partially supported by
an unrestricted educational grant from
Lundbeck Italia S.p.A., which is hereby gratefully acknowledged.

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