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2. McRae TW. The impact of computers on accounting. London: Wiley, 1964.
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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Nonsocial and social cognitive function in psychosis: interrelationships, specificity and innovative approaches

In this issue of the journal, Green et al[1] present an excellent overview of impairments in nonsocial and social cognition in schizophrenia. They raise several key questions that are in need of further theoretical and methodological work.

One such question is the nature of the relationship between nonsocial and social cognition in general, and in schizophrenia more specifically. Green et al focus on these as separable constructs with differing psychological and neurological correlates. There is certainly ample evidence for meaningful distinctions between nonsocial and social cognition, with robust data about the engagement of different neural systems by tasks that focus more on one versus the other. Further, there is evidence that deficits in nonsocial and social cognition account for at least some independent variance in functional outcome in schizophrenia. However, there are also moderate to strong correlations between nonsocial and social cognition in schizophrenia[2]. Moreover, the intriguing data showing that social cognition mediates, at least in part, the relationship between nonsocial cognition and functional outcome suggest that at least some of the deficits in nonsocial cognition serve as building blocks (or barriers) to social cognitive function, and that there may be more synergy in attempts to treat both deficits simultaneously than previously emphasized.

This thinking about the ways in which different impairments interrelate and may mediate each other extends to the growing work on motivation discussed by Green et al. They note evidence that impairments in motivation or beliefs about one's inability to successfully carry out certain cognitive functions may partially mediate the relationship between nonsocial cognition and life function. Such results raise issues such as: To what extent living with cognitive impairment reduces motivation and creates negative beliefs? What components of motivational impairments might be independent of deficits in cognitive function? Would more integrated treatment approaches that tackle multiple levels of impairment simultaneously show more evidence for efficacy?

A second question is the status of cognition in schizophrenia versus psychopathology more broadly. Green et al describe cognitive deficits as a "core feature" of schizophrenia, which is central to understanding many aspects of risk and life function in that condition. However, these deficits are not a core feature in the sense of being selective to schizophrenia. It is becoming increasingly clear that many forms of psychopathology involve impairments in cognition. Green et al note this, but focus somewhat more on the differences across disorders than on the similarities. One could argue that the most robust evidence indicates similar profiles of cognitive impairment across disorders that involve psychosis, including schizophrenia, schizoaffective disorder, bipolar disorder with psychosis, and even psychotic depression[3-5]. The severity of these deficits often vary across illnesses, with the most severe in schizophrenia, but the general pattern is often remarkably similar[3,4]. Moreover, there is also evidence for impairment in at least some cognitive domains in a host of other forms of psychopathology, including non-psychotic major depression[6] and attention-deficit/hyperactivity disorder[7].

In fact, it has been argued that impairments in cognitive domains such as executive function, working memory, or cognitive control might form a more general risk factor for mental illness, perhaps being part of the "p factor" of shared risk for psychopathology[8]. If cognitive impairments, especially in domains thought to be critical for behavioral and emotional regulation, are part of a more general risk factor for psychopathology, we need to rethink their role in the development of psychotic disorders. This would not make cognitive deficits any less important for understanding the etiology, course or outcome of schizophrenia, but it would suggest a change in our thinking about causal factors and treatment interventions that may be much more widely applicable across forms of psychopathology.

A third question is how best to ameliorate deficits in either nonsocial or social cognition in schizophrenia. Green et al provide a nice review of the relevant literature, highlighting areas of both promise and concern. They note that remediation approaches have shown moderate effect sizes for improvement of both social and nonsocial domains, with the latter seeming to be most benefited when cognitive training is coupled with psychiatric rehabilitation. However, one can also read this literature in a much less positive light. Recent meta-analyses of cognitive remediation for nonsocial cognition suggest very modest effect sizes[9], and even effect sizes of a Cohen's d of .60 or .70 are likely too modest to make a meaningful and long-lasting impact on the lives of individuals with schizophrenia.

Green et al note features of cognitive impairment in schizophrenia that should lead us to question our focus on treating individuals who already have diagnosable illnesses or even prodromal symptoms. Specifically, cognitive impairment likely precedes the onset of psychosis by many years, and may be present even early in childhood. It seems highly unlikely that we can make significant inroads on improving cognitive function among individuals whose developmental trajectories have been disrupted by long-lasting and early occurring cognitive dysfunction. Instead, we may need to think about intervention approaches that can be applied much earlier in life, starting potentially in childhood, so as to help individuals shift back to a more typical developmental trajectory that may prevent the type of functional impairment often associated with schizophrenia.

The concern with such an approach has always been that we do not have any sufficiently predictive way to identify children who are likely to be at risk for psychosis. However, this is where the suggestion that at least some types of cognitive impairment

may be much broader risk factors for psychopathology comes into play. We need not be as concerned about identifying children who are *specifically* on a risk trajectory for psychosis if we think that impairments in domains such as cognitive control, executive function, or working memory serve as more general risk factors for psychopathology.

It is still absolutely critical to consider risk-benefit tradeoffs with even general risk factors. However, should we be able to develop non-invasive approaches that enhance these domains of cognition earlier in childhood or adolescence, we would be less concerned about whether such interventions have a protective effect against psychosis specifically, and more satisfied with either an overall reduction in risk for psychopathology, regardless of its manifestation, or an overall improvement in function even amongst those who still develop psychopathology.

While some might regard this suggestion as naive or unrealistic, I would argue that we need to consider fundamentally innovative approaches to treating or preventing cognitive impairment associated with all forms of mental illness, as years of research and countless treatment studies have yet to provide pathways that are sufficiently helpful once individuals develop severe psychiatric symptoms. It is time for us to think in ways that are much more "out of the box" and to use what the data are telling us about the developmental origins of cognitive deficits to identify the timing for intervention that is most likely to yield long-lasting and meaningful benefits.

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The "online brain": how the Internet may be changing our cognition

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The impact of the Internet across multiple aspects of modern society is clear. However, the influence that it may have on our brain structure and functioning remains a central topic of investigation. Here we draw on recent psychological, psychiatric and neuroimaging findings to examine several key hypotheses on how the Internet may be changing our cognition. Specifically, we explore how unique features of the online world may be influencing: a) attentional capacities, as the constantly evolving stream of online information encourages our divided attention across multiple media sources, at the expense of sustained concentration; b) memory processes, as this vast and ubiquitous source of online information begins to shift the way we retrieve, store, and even value knowledge; and c) social cognition, as the ability for online social settings to resemble and evoke real-world social processes creates a new interplay between the Internet and our social lives, including our self-concepts and self-esteem. Overall, the available evidence indicates that the Internet can produce both acute and sustained alterations in each of these areas of cognition, which may be reflected in changes in the brain. However, an emerging priority for future research is to determine the effects of extensive online media usage on cognitive development in youth, and examine how this may differ from cognitive outcomes and brain impact of uses of Internet in the elderly. We conclude by proposing how Internet research could be integrated into broader research settings to study how this unprecedented new facet of society can affect our cognition and the brain across the life course.

Key words: Internet, cognition, attention, memory, social structures, social media, addiction, virtual reality

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The Internet is the most widespread and rapidly adopted technology in the history of humanity. In only decades, Internet use has completely re-invented the ways in which we search for information, consume media and entertainment, and manage our social networks and relationships. With the even more recent advent of smartphones, Internet access has become portable and ubiquitous to the point at which the population of the developed world can be considered "online"[1-3].

However, the impact that this new channel for connection, information, communication, and screen time is having on our brains and cognitive functioning is unclear. Prior to the Internet, a large body of research had convincingly demonstrated that the brain is somewhat malleable to environmental demands and stimuli, particularly with regards to learning new processes, due to its capacity for neuroplasticity[4]. Various scenarios have been observed to induce long-term changes in the neuronal architecture of the human brain, including second-language acquisition[5], learning new motor skills (such as juggling)[6], and even formal education or exam preparation[7]. The widespread use of the Internet across the globe has introduced, for many, the necessity and opportunity to learn a myriad of new skills and ways to interact with society, which could bring about neural changes. As an example, even simple interactions with the Internet through the smartphone's touchscreen interface have been demonstrated to bring about sustained neurocognitive alterations due to neural changes in cortical regions associated with sensory and motor processing of the hand and thumb[8]. Beyond this, the Internet also presents a novel platform for almost-endless learning of new information and complex processes, relevant to both the online and offline world[9].

Along with neuroplastic mechanisms, other environmental and biological factors can also cause changes in the brain's structure and function, resulting in cognitive decline[10]. In aging samples, for instance, there is evidence to indicate that age-related cognitive decline may be partly driven by a process of atrophy. Some studies have shown that adopting a less engaging lifestyle across the lifespan may accelerate loss of cognitive function[11], due to lower "cognitive reserve" (the ability of the brain to withstand insult from age and/or pathology)[12]. Some emerging evidence indicates that disengaging from the "real world" in favor of virtual settings may similarly induce adverse neurocognitive changes. For example, a recent randomized controlled trial (RCT)[13] found that six weeks of engaging in an online role playing game caused significant reductions in grey matter within the orbitofrontal cortex – a brain region implicated in impulse control and decision making. However, the study did not address the extent to which these results were specific to online gaming, rather than general internet usage. Nonetheless, this raises the possibility that various types of Internet usage could differentially affect the brain and cognitive processes – in both adverse and beneficial ways. This may be of particular relevance to the developing brains of children and adolescents, as many cognitive processes (particularly those relevant to higher executive functions and social cognition)

are not entirely innate, but rather are strongly influenced by environmental factors[14].

Although only recently emerging, this possibility has led to a substantial body of research empirically investigating the multiple potential pathways through which the Internet could affect our brains' structure, function, and cognitive development. Specifically, the bulk of existing research can be separated into three specific domains, examining how the internet is affecting: a) attention (i.e., how the constant influx of online information, prompts and notifications competing for our attention may encourage individuals to displace their concentration across multiple incoming media streams – and the consequences this may have for attentional-switching versus sustained-attention tasks); b) memory and knowledge (i.e., the extent to which we rely on the Internet as our primary informational resource, and how unique properties of online information access may affect how we process new memories and value our internal knowledge); c) social cognition (along with the personal and societal consequences of increasingly embedding our social networks, interactions, and status within the online world).

In this state-of-the-art review, we present the current leading hypotheses of how the Internet may alter these cognitive processes, subsequently examining the extent to which these hypotheses are supported by recent findings from psychological, psychiatric and neuroimaging research. In this way, we aggregate the contemporary evidence arising from multiple fields of research to produce revised models on how the Internet may be affecting our brains and cognition. Furthermore, whereas studies to date have focused upon only specific age groups, we examine the effects of the Internet on the human brain across the entire life course. In particular, we explore how the potential benefits/drawbacks of extensive Internet integration with cognitive processes may differ among children and older adults. Finally, we identify important gaps in the existing literature to present key priorities for future research in order to gain new insights for minimizing detrimental effects of the Internet, while capitalizing on this new feature of our societies to potentially influence neurocognitive processes in a beneficial way.

"DIGITAL DISTRACTIONS": A HIJACK OF ATTENTION ON THE INFORMATION HIGHWAY?

How does the Internet gain and sustain our attention?

The Internet consumes a considerable chunk of our attention on a day-to-day basis. The vast majority of adults go online daily, and over a quarter report being online "almost constantly"[2]. Within this, one in five American adults are now "smartphone-only" Internet users[1]. Importantly, the introduction of these Internet-enabled mobile devices has also reduced the "digital divide" previously experienced by lower and middle income countries[15]. The amount and frequency of Internet usage is even more pronounced amongst younger people. Most adults today witnessed the beginning of the transition from "Internet-free" to "Internet-everywhere" societies. However, younger generations (termed "digital natives"[16]) have been brought up entirely within a "connected world", particularly in developed countries. Consequently, digital natives are often the first to adopt new online technologies as they arise[16], and engage extensively with all existing features of the Internet. For instance, 95% of US teens have access to a smartphone, and 45% are online "almost constantly"[3].

Multiple factors are driving the rapid uptake and extensive usage of Internet-enabled technologies across the globe. This is partly due to the Internet now being unavoidable, ubiquitous, and a highly functional aspect of modern living. For instance, Internet use is now deeply entwined with education, travel, socializing, commerce, and the majority of workplaces. Along with pragmatic uses, the Internet also offers an endless array of recreational and entertainment activities, through podcasts, e-books, videos, streaming movies and gaming. However, the ability of the Internet to capture and hold attention is not solely due to the quality of media content available online. Rather, it is also driven by the underlying design and presentation of the online world. One such example is the self-evolving "attraction mechanism"; whereby aspects of the Internet that fail to gain attention are quickly drowned out in the sea of incoming information, while the successful aspects of the adverts, articles, apps or anything that does manage to capture our attention (even superficially) are logged (through clicks and scrolls), noticed (through online shares), and subsequently proliferated and expanded upon. Alongside this, leading technology companies have been accused of intentionally capitalizing on the addictive potential of Internet, by studying, testing, and refining the attention-grabbing aspects of their websites and applications ("apps") to promote extremely high levels of engagement, without due concern for user well-being[17].

Furthermore, even when not using the Internet for any specific purpose, smartphones have introduced widespread and habitual "checking" behaviours, characterized by quick but frequent inspections of the device for incoming information from news, social media, or personal contacts[18]. These habits are thought to be the result of behavioural reinforcement from "information rewards" that are received immediately on checking the device[19], potentially engaging the cortico-striatal dopaminergic system due to their readily available nature[20]. The variable-ratio reinforcement schedule inherent to device checking may further perpetuate these compulsive behaviours[21].

Cognitive consequences of the attention-grabbing Internet

The unprecedented potential of the Internet to capture our attention presents an urgent need for understanding the impact that this may have on our thought processes and well-being. Already, education providers are beginning to perceive detrimental effects of the Internet on children's attention, with over 85% of teachers endorsing the statement that "today's digital

technologies are creating an easily distracted generation"[22]. The primary hypothesis on how the Internet affects our attentional capacities is through hyperlinks, notifications, and prompts providing a limitless stream of different forms of digital media, thus encouraging us to interact with multiple inputs simultaneously, but only on a shallow level, in a behavioural pattern termed "media multi-tasking"[23,24].

The seminal study by Ophir et al[23] was among the first to explore the sustained impact of media multi-tasking on cognitive capacities. This was a cross-sectional study of individuals who engaged in "heavy" (i.e., frequent and extensive) media multi-tasking compared to those who did not. Cognitive testing of the two groups produced the then-surprising finding that those involved in heavy media multi-tasking performed worse in task-switching tests than their counterparts – contrary to the authors' expectation that the "extra practice" afforded by frequent media multi-tasking would confer cognitive benefit in task-switching scenarios. Closer inspection of findings suggested that the impeded task-switching ability in heavy media multi-tasking individuals was due to their increased susceptibility to distraction from irrelevant environmental stimuli[23].

Since these initial findings, the effects of media multi-tasking on cognition have come under increasing scrutiny, because the increasingly diverse forms of entertainment and activities available through the online world can further our capabilities (and temptation) of engaging in media multi-tasking[25], even on single devices. For instance, Yeykelis et al[26] measured participants' media multi-tasking between different types of online media content while using just one device (personal laptops), and found that switches occurred as frequently as every 19 seconds, with 75% of all on-screen content being viewed for less than one minute. Measures of skin conductance during the study found that arousal increased in the seconds leading up to media switching, reaching a high point at the moment of the switch, followed by a decline afterward[26]. Again, this suggests that the proclivity for alternating between different computer windows, opening new hyperlinks, and performing new searches could be driven by the readily available nature of the informational rewards, which are potentially awaiting in the unattended media stream. Supporting this, the study also found that, whereas switching from work-related content to entertainment was associated with increased arousal in anticipation of the switch, there was no anticipatory arousal spike associated with entertainment to work-content switches[26].

The growing concern around the increasing amount of media multi-tasking with the spread of ubiquitous Internet access has resulted in further empirical studies. These have produced conflicting findings, with some failing to find any adverse effects on attention[27], and others indicating that media multi-tasking may even be linked to increased performance for other aspects of cognition, such as multisensory integration[28]. Nonetheless the literature, on balance, does seem to indicate that those who engage in frequent and extensive media multi-tasking in their day-to-day lives perform worse in various cognitive tasks than those who do not, particularly for sustained attention[25].

Imaging studies have shed light onto the neural differences which may account for these cognitive deficits. Functionally, those who engage in heavy media multi-tasking perform poorer in distracted attention tasks, even though exhibiting greater activity in right prefrontal regions[29]. As right prefrontal regions are typically activated in response to distractor stimuli, the observed increases in recruitment of these regions alongside poorer performance suggests that heavy media multi-taskers require greater cognitive effort to maintain concentration when faced with distractor stimuli[29]. Structurally, high levels of Internet usage[30] and heavy media multi-tasking[31] are associated with decreased grey matter in prefrontal regions associated with maintaining goals in face of distraction (such as the right frontal pole and anterior cingulate cortex). However, the findings to date must be interpreted with caution, as various confounding factors may be affecting the results of these cross-sectional imaging studies. Although the differences persist when controlling for general digital media use and other simple confounders (age, gender, etc.), further research is required to examine if the observed neural differences are specifically attributable to heavy vs. light media multi-tasking, or in fact driven by broader differences in lifestyle between the two groups.

Given the amount of time that people now spend in media multi-tasking via personal digital devices, it is increasingly relevant to consider not only sustained changes which arise in those who engage in large amounts of media multi-tasking, but also the acute effects on immediate cognitive capacities. A meta-analysis of 41 studies showed that engaging in multi-tasking was associated with significantly poorer overall cognitive performance, with a moderate-to-large effect size (Cohen's d=–0.71, 95% CI: –0.86 to –0.57). This has been confirmed by more recent studies, further showing that even short-term engagement with an extensively hyperlinked online environment (i.e., online shopping for 15 minutes) reduces attentional scope for a sustained duration after coming offline, whereas reading a magazine does not produce these deficits[32].

Overall, the available evidence strongly indicates that engaging in multi-tasking via digital media does not improve our multi-tasking performance in other settings – and in fact seems to decrease this cognitive capacity through reducing our ability to ignore incoming distractions. Much of the multi-tasking investigations so far have been focusing on personal computers. However, smartphone technologies may even further encourage people to engage in media multi-tasking through high rates of incoming prompts from emails, direct messages and social media notifications occurring while both using and not using the device. Thus, along with determining long-term consequences of media multi-tasking, future research should examine how the constant multi-tasking made possible by Internet-enabled mobile devices may impact daily functioning through acute but high frequency effects.

Furthermore, both the immediate and chronic effects of media multi-tasking are relatively unexplored in children and adolescents, who are the prime users of such technologies[33] and are at a phase of development that is crucial for refining

higher cognitive abilities[14]. The first longitudinal study of media multi-tasking in young people has recently found that frequent multi-tasking behaviours do predict the development of attentional deficits specifically in early adolescents, but not in older teens[34]. Additionally, extensive media multi-tasking during childhood and adolescence could also negatively impact cognitive development through indirect means, by reducing engagement with academic and social activities, as well as by interfering with sleep[35], or reducing the opportunity to engage in creative thinking[36,37]. Clearly, further research is necessary to properly measure the effects of ubiquitous computing on children's cognitive development, and to find practical ways for ameliorating any detrimental impact this may be having.

"iFORMATION": NEUROCOGNITIVE RESPONSES TO ONLINE INFORMATION GATHERING

The Internet and transactive memory

In response to the question "How has the Internet changed your life?", some common answers include finding new friends, renewing old friendships, studying online, finding romantic relationships, furthering career opportunities, shopping, and travel[38]. However, the most common answer is people stating that the Internet has "changed the way in which they access information"[38]. Indeed, for the first time in human history, the majority of people living in the developed world have access to almost all factual information in existence literally at their fingertips.

Along with the obvious advantages, this unique situation also introduces the possibility of the Internet ultimately negating or replacing the need for certain human memory systems – particularly for aspects of "semantic memory" (i.e., memory of facts) – which are somewhat independent from other types of memory in the human brain[39]. An initial indication of Internet information gathering affecting typical memory processes was provided by Sparrow et al[40], who demonstrated that the ability to access information online caused people to become more likely to remember where these facts could be retrieved rather than the facts themselves, indicating that people quickly become reliant on the Internet for information retrieval.

It could be argued that this is not unique to the Internet, but rather just an example of the online world acting as a form of external memory or "transactive memory"[40,41]. Transactive memory has been an integral part of human societies for millennia, and refers to the process by which people opt to outsource information to other individuals within their families, communities, etc., such that they are able to just remember the source of the knowledge, rather than attempting to store all of this information themselves[41]. Although beneficial at a group level, using transactive memory systems does reduce an individual's ability to recall the specifics of the externally stored information[42]. This may be due to individuals using transactive memory for "cognitive offloading", implicitly reducing their allocation of cognitive resources towards remembering this information, since they know this will be available for future reference externally. This phenomenon has been demonstrated in multiple contexts, including those of team work[43] and other "non-Internet" technologies (e.g., photography reducing individuals' memories of the objects they photographed)[44].

However, it is becoming clear that the Internet actually presents something entirely novel and distinct from previous transactive memory systems[45,46]. Crucially, the Internet seems to bypass the "transactional" aspect that is inherent to other forms of cognitive offloading in two ways. First, the Internet does not place any responsibility on the user to retain unique information for others to draw upon (as would typically be required in human societies)[45]. Second, unlike other transactive memory stores, the Internet acts as a single entity that is responsible for holding and retrieving virtually all factual information, and thus does not require individuals to remember what exact information is externally stored, or even where it is located. In this way, the Internet is becoming a "supernormal stimulus"[46] for transactive memory – making all other options for cognitive offloading (including books, friends, community) become redundant, as they are outcompeted by the novel capabilities for external information storage and retrieval made possible by the Internet.

How does a supernormal stimulus interact with normal cognition?

Unfortunately, the rapid methods of acquisition and constant availability of information afforded by the Internet may not necessarily lead to better use of information gained. For instance, an experimental study[47] found that individuals instructed to search for specific information online completed the information gathering task faster than those using printed encyclopedias, but were subsequently less able to recall the information accurately.

During Internet and encyclopedia information gathering tasks, functional magnetic resonance imaging was used to examine activation in the ventral and dorsal streams. These regions are referred to as the "what" and "where" streams, respectively, due to their indicated roles in storing either the specific content (ventral stream) or external location (dorsal stream) of incoming information[47]. Although there was no difference in activation of the dorsal stream, results showed that the poorer recall of Internet-sought information compared to encyclopedia-based learning was associated with reduced activation of the ventral ("what") stream during online information gathering. These findings further support the possibility, initially raised by Sparrow et al[40], that online information gathering, while faster, may fail to sufficiently recruit brain regions for storing information on a long-term basis.

The potential for online searching to produce a sustained impact upon our cognitive processes has been investigated in a series of studies examining pre-post changes following a

six-day Internet search training paradigm. In these studies, young adults were given an hour per day of Internet search tasks, and undertook an array of cognitive and neuroimaging assessments pre- and post-training. Results showed that the six-day Internet search training reduced regional homogeneity and functional connectivity of brain areas involved in long-term memory formation and retrieval (e.g., temporal gyrus)[48]. This indicates that a reliance on online searching may impede memory retrieval by reducing the functional connectivity and synchronization of associated brain regions[48]. Furthermore, when faced with new questions after the six days, the training had increased participants' self-reported impulses towards using the Internet to answer those questions, which was reflected in a recruitment of prefrontal brain areas required for behavioural and impulse control[49]. This increased propensity for relying on Internet searches for gathering new information has been replicated in subsequent studies[50], and is in keeping with the "supernormal stimulus" nature of the Internet, potentially suggesting that online information gathering quickly trains people to become dependent on this tool when faced with unknown issues.

However, despite the possible adverse effects on regular "offline" memory, the six-days training did make people more efficient at using the Internet for retrieving information, as participants became faster at the search tasks, with no loss of accuracy[51]. Search training also produced increases in white matter integrity of the fiber tracts connecting the frontal, occipital, parietal and temporal lobes, significantly more than the non-search control condition[52]. In other studies, cognitive offloading via digital devices has also been found to improve people's ability to focus on aspects that are not immediately retrievable, and thus remember these better in the future[53].

These findings seem to support the emergent hypotheses that relying on the Internet for factual memory storage may actually produce cognitive benefit in other areas, perhaps by "freeing up" cognitive resources[54], and thus enabling us to use our newly available cognitive capacities for more ambitious undertakings than previously possible[45]. Researchers advocating this view have pointed to multiple domains of collective human endeavor that have already been transformed by the Internet's provision of supernormal transactive memory, such as education, journalism and even academia[55]. As online technologies continue to advance (particularly with regards to "wearables"), it is conceivable that the performance benefits from the Internet, which are already visible at the societal level, could ultimately become integrated within individuals themselves, enabling new heights of cognitive function[56].

Unfortunately, however, a more sobering finding with regards to the immediate possibility of ubiquitous Internet access enabling new heights of human intelligence is provided by Barr et al[57], who observed that analytical thinkers, with higher cognitive capacities, actually use their smartphone less for transactive memory in day-to-day situations compared to individuals with non-analytical thinking styles. Furthermore, the reduced smartphone usage in analytical versus non-analytical thinkers was specific to online information searching, with no differences in social media or entertainment usages, thus indicating that the differences are likely due to the Internet furthering "cognitive miserliness" among less analytical thinkers[57].

Alongside this, the increasing reliance on the Internet for information may cause individuals to "blur the lines" between their own capabilities and their devices'[58]. In a series of experiments, Fisher et al[59] investigated how the Internet influences our self-perceived knowledge. Results showed that online searching increases our sense of how much we know, even though the illusion of self-knowledge is only perceived for the domains in which the Internet can "fill in the gaps" for us. The experiments also demonstrated how quickly individuals internalized the Internet's external knowledge as their own – as even immediately after using the Internet to answer the task questions, participants attributed their higher quality explanations to "increased brain activity". More recent studies have shown that illusions of self-knowledge similarly persist when using smartphones to retrieve online information[58]. As individuals become more and more connected with their personal digital devices (which are also always accessible), it seems inevitable that the distinction between self and Internet's abilities will become increasingly elusive, potentially creating a constant illusion of "greater than actual knowledge" among large portions of the population.

Overall, the Internet clearly can provide a "superstimulus" for transactive memory, which is already changing the way we store, retrieve, and even value knowledge. However, with popular online information sources such as Google and Wikipedia less than 20 years old, it is currently not possible to ascertain how this may eventually be reflected in long-term changes to the structure and function of the human brain. Nonetheless, our constant connection with the online world through personal devices (i.e., smartphones), along with the emerging potential for more direct integration through wearable devices, certainly indicates that we are set to become more reliant on the Internet for factual information as time goes on. Also, whereas the studies described above have focused on factual knowledge, the Internet is also now becoming a superstimulus for spatial information (through providing constant access to online maps and global positioning system). As spatial memory is somewhat independent from semantic memory in the human brain[60], further research should investigate the multitude of ways in which extensive use of these external memory systems may reduce, enhance or alter our cognitive capacities.

ONLINE SOCIAL NETWORKS: FAULTY CONNECTIONS, OR FALSE DICHOTOMY?

Human sociality in the online world

Social relationships and having a sense of connection are important determinants of happiness and stress relief[61,62], mental and physical well-being[63,64], and even mortality[65]. Over the past decade, the proportion of an individual's social

interactions that take place online within social networking sites (e.g., Facebook, Instagram, Twitter) has grown dramatically[66,67], and our connection with these sites is now strongly meshed with the offline world. The real-world implications of this are perhaps best evidenced by the critical role that social media have played in multiple global affairs, including reportedly starting and precipitating the London Riots, the Occupy movement[68], and even the Arab Spring[69], along with potentially influencing the outcomes of the UK's European Union Referendum ("Brexit")[70] and the 2016 US elections[71]. Clearly, understanding the shift from real-world interactions into the online social environment (and vice versa) holds significance to almost all aspects of people's lives.

Our motivations towards using social media is broadly similar to the instinctual desires underlying "real world" social interactions, as people are drawn to online sociality in order to exchange information and ideas, along with gaining social support and friendships[72]. However, whether or not these virtual interactions engage the human brain in ways analogous to real-world socialization remains a topic of debate since the turn of the century[73]. Whereas it would be highly beneficial if social media sites could fulfil the implicit human needs for social connection, it may be that the distinction between online and offline networks is so great that entirely different cognitive domains are involved in navigating these different environments[74,75].

How does the online environment affect our fundamental social structures?

To investigate the neuroimaging correlates of offline and online networks, the seminal study by Kanai et al[74] collected real-world social network size, online sociality (i.e., Facebook friends) and magnetic resonance imaging scans from 125 participants. Results showed that both real-world social network size and number of Facebook friends were significantly associated with amygdala volume. As this has previously been established as a key brain region for social cognition and social network size[76], these results present a strong case for the overlap between online and offline sociality in the human brain.

However, those authors also found that the grey matter volume of other brain regions (specifically, posterior regions of the middle temporal gyrus and superior temporal sulcus, and the right entorhinal cortex) were predicted by the numbers of participants' Facebook friends, but held no relationship to their real-world social networks. This suggests that certain unique aspects of social media implicate aspects of the brain that are not central in "real-world" social settings. For instance, the tendency for online networks to encourage us towards holding many weak social connections, involving thousands of face-to-name pairs, could require high associative memory capacities, which is not typically required in real-world networks (as these are comprised of fewer, but more familiar, relationships)[74]. As associative memory formation for name-face pairs involves the right entorhinal cortex[77,78], this could explain the exclusive relationship that this region holds with online social (but not real-world) network size[74].

Indeed, one key difference which may separate how the brain handles online and offline social networks is the unique capacity afforded by the Internet for people to hold, and simultaneously interact with, millions of "friendships"[79,80]. Empirical testing of this hypothesis is a most fruitful area of investigation stemming from research into the fundamental similarities and differences between these two social worlds at a biological level[66]. When defining "friendships" under a broad context (people who maintain contact and share an emotional bond)[66], two patterns are prominent across a diverse range of real-world social networks: a) the average individual has around 150 "friendships" (but this is highly variable between individuals), and b) this is made up of five hierarchical layers, consisting of primary partners, intimate relationships, best friends, close friends, and all friends, which follow a size-scaling ratio of around 3 (i.e., each cumulative layer is 3 times bigger than the last), and therefore have set average (cumulative/inclusive) sizes of 1.5, 5, 15, 50 and 150 respectively[66]. The patterns of the average number of 150 total friendship connections, and the scaling sizes of the five hierarchical layers of relationships making this up, have been found across regions and time periods within various human organizations, ranging from hunter-gatherer societies[81,82] and historical village populations[83], armies[66], residential camps[84], to personal networks of modern Europeans[85].

Thus, given the unprecedented potential that online social networks allow in terms of number of connections, and the varied contexts these take place over[79,80], it is imaginable that this extraordinary environment may allow these two apparently set aspects of real-world social networks to be bypassed. However, recent findings have confirmed that user-to-user friendship connections, posting patterns and exchanges within Twitter, Facebook, and even online gaming platforms, all indicate a similar average number of general friendships (around 150, despite high skew), along with maintaining the same scaled sizes of the hierarchical structure of the five distinct friendship layers (as determined by reciprocal communication exchanges)[86-89]. Therefore, even within the unique realms of online social networks, the most fundamental operations of human social networks appear to remain relatively unchanged[88,89]. So, it is highly conceivable that the social connections formed in the online world are processed in similar ways to those of the offline world, and thus have much potential to carry over from the Internet to shape "real-world" sociality, including our social interactions and our perceptions of social hierarchies, in ways that are not restricted to the context of the Internet.

The driving forces that sustain the set structural patterns of social networks, even when faced with the immense connective potential of the online world, may be broadly explained by two overlapping mechanisms. First, constraints on social cognition within the human brain seem to carry over across social contexts[66]. For instance, humans struggle to engagingly

interact with more than three individuals simultaneously in the real world, and this limitation on attention also appears to apply online[90,91]. This evidence is in agreement with the hypothesis that circumventing the cognitive constraints on social relationships may be difficult even when technology affords unnatural opportunities to do so[88].

The second driver of set boundaries on social activity is that simple underlying factors may produce social constraints, even within online settings. Most obviously, investment in social relationships is limited by time constraints, and this may contribute to the set patterns of both the number and type of social connections[93,94]. In line with this, analyses across various social contexts have shown that temporal limitations govern the number of social interactions that individuals engage in, and how they distribute these across their different kinds of relationships[93,94]. Again, these general interaction rates remain similar within online social networks[87,88].

The possibility that the parameters on all social networks (online or offline) are governed by basic underlying factors is further supported by research showing that similar structures also exist within simpler social systems, such as animal societies[66,95]. For instance, the sizes and scaling of hierarchical "friendship" layers found in online and offline human networks are also found in dolphins, elephants, and various primate species[96], and the phenomena of humans increasing the number and strength of their social networks connections following the death of a friend on Facebook[97] is also seen in wild birds, which show compensatory up-regulation of their social network connections upon experiencing the loss of a social associate[98].

Supporting the idea that limited cognitive capacities govern our social structures is research showing that the brain regions predicting individual variation in social network size in humans also do so for macaques[99]. Strong support for simple underlying factors (such as time) governing our general patterning of social interactions can be found in studies demonstrating that entirely computationally simulated systems replicate some of the apparent complexities of human social networks, even under relatively simple rules[100,101]. Examples include agent-based models generating similar social layering structures as humans when sociality is defined as time-limited[100].

In light of the current evidence regarding how the Internet may have affected human thinking surrounding social networks, it is undeniable that the online environment poses unique potential and context for social activity[79,80,102,103], which may invoke some non-identical cognitive processes and brain areas in comparison to the offline world[74,75]. Nevertheless, aside from these comparatively fine-scale differences, it appears that our brains process the online and offline social networks in surprisingly similar ways, as demonstrated by the shared cognitive capacities and simple underlying factors ultimately governing their fundamental structure[87,88]. As such, the online social world has very significant implications for not only measuring and understanding human sociality, but also for governing the outcomes of social processes across various aspects of life.

Social cognitive responses to the online social world

Given the evidence above, an appropriate metaphor for the relationship between online and real-world sociality could be a "new playing field for the same game". Even beyond the fundamental structure, emerging research suggests that neurocognitive responses to online social occurrences are similar to those of real-life interactions. For instance, being rejected online has been shown to increase activity in brain regions strongly linked with social cognition and real-world rejection (medial prefrontal cortex[104]) in both adults and children[105-107]. However, within the "same old game" of human sociality, online social media is bending some of the rules – potentially at the expense of users[17]. For instance, whereas real-world acceptance and rejection is often ambiguous and open to self-interpretation, social media platforms directly quantify our social success (or failure), by providing clear metrics in the form of "friends", "followers", and "likes" (or the potentially painful loss/absence of these)[107]. Given the addictive nature of this immediate, self-defining feedback, social media companies may even capitalize upon this to maximally engage users[17]. However, growing evidence indicates that relying on online feedback for self-esteem can have adverse effects on young people, particularly those with low social-emotional well-being, due to high rates of cyberbullying[108], increased anxiety and depression[109,110], and increased perceptions of social isolation and exclusion among those who feel rejected online[111].

Another process common to human social behaviour in both online and offline worlds is the tendency to make upward social comparisons[112,113]. Whereas these can be adaptive and beneficial under regular environmental conditions[112], this implicit cognitive process can also be hijacked by the artificial environmental manufactured on social media[113,114], which showcases hyper-successful individuals constantly putting their best foot forward, and even using digital manipulation of images to inflate physical attractiveness. By facilitating exposure to these drastically upward social comparisons (which would rarely be encountered in everyday life), online social media can produce unrealistic expectations of oneself – leading to poor body image and negative self-concept, particularly for younger people[107,111,115,116]. For instance, in adolescents (particularly females), those who spent more time on social media and smartphones have a greater prevalence of mental health problems, including depression, than those who spent more time on "non-screen" activities[116], with greater than 5 hrs/day (versus 1 hr/day) associated with a 66% increased risk of one suicide-related outcome[117].

However, a causal relationship between high levels of social media use and poorer mental health is currently difficult to establish, as there is most likely a complex interaction between several confounding factors, including reduced sleep and in-person social interaction, and increased sedentary behaviour and perceived loneliness[116,118]. Nonetheless, given the large amounts of social media use observed among young people, future research should thoroughly examine the potentially

detrimental effects that this new setting for sociality may have on health and well-being, along with aiming to establish the driving factors – such that adjustments can be made in subsequent iterations of social media in order to produce more positive outcomes.

Whereas young people with mental disorders may be the most vulnerable to negative input from social media, these media may also present a new platform for improving mental health in this population, if used correctly. In future, social media may also be exploited to promote ongoing engagement with Internet-based interventions, while addressing key (but frequently neglected) targets such as social connectedness, social support and self-efficacy, to aim to bring about sustained functional improvements in severe and complex mental health conditions[119]. To achieve these goals, online social media-based interventions need to be designed to promote engagement by harnessing, in an ethical and transparent manner, effective strategies used by the industry. For instance, developing technologies which are increasingly adopted by online marketing and tech companies, such as natural language processing, sentiment analyses and machine learning, could be capitalized upon, for example making it possible to identify those at increased risk for suicide or relapse[120], and rationalizing human driven support to those who need it most at the time they need it[121]. In addition, online systems will be able to learn from what helps individuals and when, opening a window into personalized, real time interventions[121].

While the use of online social media-based interventions is in its infancy, pioneering efforts indicate that these interventions are safe, engaging, and have the potential to improve clinical and social outcomes in both patients and their relatives[122-127]. That said, online interventions have failed up to now to be adopted by mental health services[128,129]. The main reasons include high attrition rates, poor study designs which reduce translational potential, and a lack of consensus around the required standards of evidence for widespread implementation of Internet-delivered therapies[130-132]. Efforts are currently underway to determine the long-term effects of the first generation of social media-based interventions for mental illness via large randomized controlled trials[133,134]. Alongside this clinical use, developing public health strategies for young adults in the general population to avoid the potential adverse effects and negative aspects of typical social media are also warranted.

CONCLUSIONS AND DIRECTIONS

As digital technologies become increasingly integrated with everyday life, the Internet is becoming highly proficient at capturing our attention, while producing a global shift in how people gather information, and connect with one another. In this review, we found emerging support for several hypotheses regarding the pathways through which the Internet is influencing our brains and cognitive processes, particularly with regards to: a) the multi-faceted stream of incoming information encouraging us to engage in attentional-switching and "multi-tasking", rather than sustained focus; b) the ubiquitous and rapid access to online factual information outcompeting previous transactive systems, and potentially even internal memory processes; c) the online social world paralleling "real world" cognitive processes, and becoming meshed with our offline sociality, introducing the possibility for the special properties of social media to impact on "real life" in unforeseen ways.

However, with fewer than 30 years since the Internet became publicly available, the long-term effects have yet to be established. Within this, it seems particularly important that future research determines the impact of the Internet on us throughout different points in the lifespan. For instance, the Internet's digital distractions and supernormal capacities for cognitive offloading seem to create a non-ideal environment for the refinement of higher cognitive functions in critical periods of children and adolescents' brain development. Indeed, the first longitudinal studies on this topic have found that adverse attentional effects of digital multi-tasking are particularly pronounced in early adolescence (even compared to older teens)[34], and that higher frequency of Internet use over 3 years in children is linked with decreased verbal intelligence at follow-up, along with impeded maturation of both grey and white matter regions[135].

On the other hand, the opposite may be true in older adults experiencing cognitive decline, for whom the online environment may provide a new source of positive cognitive stimulation. For instance, Internet searching engaged more neural circuitry than reading text pages in Internet savvy older adults (aged 55-76 years)[9]. Furthermore, experimental studies have found that computer games available online and through smartphones can be used to attenuate aging-related cognitive decline[136-138]. Thus, the Internet may present a novel and accessible platform for adults to maintain cognitive function throughout old age. Building from this, successful cognitive aging has previously been shown to be dependent upon learning and deploying cognitive strategies, which can compensate for aging-related decline in "raw" memory capacities[139]. This has previously been referred to as optimizing internal cognitive processes (e.g., through mnemonic strategies), or taking advantage of cognitive offloading in traditional formats (list making, transactive memory, etc.)[139]. Nonetheless, as Internet-based technologies become more deeply integrated with our daily cognitive processing (through smartphones, wearables, etc.), digital natives could feasibly develop forms of "online cognition" in the aging brain, whereby older adults can increasingly take advantage of web-based transactive memory and other emerging online processes to fulfil (or even exceed) the typical capacities of a younger brain.

Although it is an emerging area of study, the same could apply for social aspects of the online world. Whereas young people seem particularly prone to the rejections, peer pressure, and negative appraisals this world may induce[107], older adults may ultimately be able to harness social media in order to overcome isolation and thus continue to benefit from the

diverse range of physical, mental and neurocognitive benefits associated with social connection[73]. Viewed collectively, the nascent research in this area already indicates that equivalent types of Internet usage may have differential effects on individuals' cognitive and social functioning depending on their point in the lifespan.

For better or for worse, we are already conducting a mass-scale experiment of extensive Internet usage across the global population. A more fine-scale analysis is essential to gaining a fuller understanding of the sustained impact of this usage across our society. This could include measuring frequency, duration and types of Internet usage as a standard part of national data projects, for instance through collecting Internet data (from either device-based or self-report measures) in "biobank" assessment protocols. Combining this with the extensive genetic, socio-demographic, lifestyle and neuroimaging data gathered by some ongoing projects, researchers could be able to establish the impact of Internet usage on psychological well-being and brain functioning across entire populations (rather than the currently limited study samples), while also controlling for multiple confounders.

Overall, this early phase of the Internet's introduction into our society is a crucial period for commencing rigorous and extensive research into how different types of Internet usage interact with human cognition, in order to maximize our opportunities for harnessing this new tool in a beneficial manner, while minimizing the potentially adverse effects.

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Mental illness and well-being: an affect regulation perspective

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Mental health crucially depends upon affective states such as emotions, stress responses, impulses and moods. These states shape how we think, feel and behave. Often, they support adaptive functioning. At other times, however, they can become detrimental to mental health via maladaptive affect generation processes and/or maladaptive affect regulation processes. Here, we present an integrative framework for considering the role of affect generation and regulation in mental illness and well-being. Our model views affect generation as an iterative cycle of attending to, appraising and responding to situations. It views affect regulation as an iterative series of decisions aimed at altering affect generation. Affect regulation decisions include identifying what, if anything, should be changed about affect, selecting where to intervene in the affect generation cycle, choosing how to implement this intervention, and monitoring the regulation attempt to decide whether to maintain, switch or stop it. Difficulties with these decisions, often arising from biased inputs to them, can contribute to manifestations of mental illness such as clinical symptoms, syndromes and disorders. The model has a number of implications for clinical assessment and treatment. Specifically, it offers a common set of concepts for characterizing different affective states; it highlights interactions between affect generation and affect regulation; it identifies assessment and treatment targets among the component processes of affect regulation; and it is applicable to prevention and treatment of mental illness as well as to promotion and restoration of psychological well-being.

Key words: Affect, affect regulation, process model, mental illness, well-being, transdiagnostic mechanisms, psychotherapy

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Someone in good mental health enjoys not only freedom from mental illness but also substantial psychological well-being. As the World Health Organization puts it, "mental health is a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community"[1].

These characteristics of mental health depend, among other things, upon affective states such as emotions, stress responses, impulses and moods. An instance of affect can be viewed as more or less healthy, depending on whether its intensity, duration, frequency or type facilitates or threatens mental health in a given context[2,3]. For example, becoming a bit anxious before a job interview can be healthy when it improves motivation and performance. Intense anxiety, by contrast, can be unhealthy when it impairs performance and contributes to avoidance of future social challenges.

Some form of unhealthy affect can be found among the defining features of 40 to 75% of mental disorders[2,4]. It is therefore important to understand how affect becomes unhealthy, and what can be done to prevent or treat unhealthy affect. These questions have long been of interest for psychology and psychiatry[5]. To mention only a few major lines of inquiry, the psychodynamic tradition has related affect to contests between desires and constraints[6]; the stress and coping tradition has elucidated cognitive antecedents and physiological consequences of affect[7,8]; and the affective neuroscience tradition has revealed some of the brain mechanisms underlying affective behaviors[9-11].

The diversity of literature on affect and mental health has resulted in a large number of poorly integrated accounts. For instance, accounts of affect in mental illness[12] tend to be separate from accounts of affect in well-being[13]. Separate accounts can also be found for similar affective phenomena in different mental illnesses[14]. Adding to the complexity, different accounts often operate on different levels of analysis, from neurochemical to psychosocial. The fragmented set of explanations for the role of affect in mental health makes it difficult for practitioners and researchers to conceptualize individual cases; to analyze transdiagnostic mechanisms; and to integrate advances from ongoing research.

One way to address these limitations is to construct integrative frameworks that explain different kinds of affect across mental illness as well as well-being. When seeking to understand how unhealthy affect arises, it is important to realize that, once *generated*, an emotion, a stress response, an impulse or a mood need not continue to dominate behavior, because people routinely use affect *regulation* to change these affective states[8,15-21]. Thus, unhealthy affect can result from problematic affect generation, problematic affect regulation, or some combination of the two.

Unhealthy affect may be said to be due to *affect regulation failure* when affect regulation is not successfully engaged to counteract maladaptive affect generation. Unhealthy affect may be said to be due to *affect misregulation* when affect regulation aggravates matters by changing affect in a maladaptive direction. Both affect regulation failure and affect misregulation can increase the risk of mental illness as well as hinder psychological well-being. Conversely, adaptive affect regulation can prevent, reverse or alleviate mental illness as well as promote well-being.

In this paper, we offer an integrative framework for thinking about the interplay between affect generation and affect regulation in mental health. We focus primarily on mental illness, but the principles we discuss are equally relevant for psychological well-being. We also focus primarily on affect regulation but, in order to understand how affect can be regulated, we also need to consider how affect is generated.

In the first two sections of the paper, we present the *process model of affect regulation,* an integrative framework that views affect generation as a four-stage process that can be altered by another four-stage process of affect regulation[15,22,23]. In the third section of the paper, we use this framework to identify affect regulation difficulties that contribute to mental illnesses, drawing examples from a variety of symptoms, syndromes and disorders. In the final section, we consider several implications of the process model of affect regulation for clinical assessment and treatment.

AFFECT GENERATION

We use "affect" as an umbrella term to denote emotions such as anxiety or joy; stress responses such as feeling threatened or feeling challenged; impulses such as an urge to flee or to have a drink; and moods such as depression or elation. Despite their differences, what these diverse processes have in common is that they all involve valuation – a good-for-me vs. bad-for-me distinction – that can shape behavior[15,24-27]. For instance, anxiety, feeling threatened, an urge to flee, and depression all signal that something is unpleasant and worth avoiding. Joy, feeling challenged, an urge to drink, and elation all signal that something is pleasant and worth approaching. Valuation reflects what a situation has to offer in relation to what the individual values, needs or wants. The function of affective states is therefore to shape behavior in accordance with the relationship between situation and motivational concerns.

Given their shared function, affective states can be analyzed using common concepts. Following a cybernetic approach[15,28-30], we view affect as a series of iterative cycles comprising four stages: a) a *situation* that can be experienced or imagined; b) *attention* that shapes how the situation is perceived; c) *appraisal* of the situation in light of motivational concerns; and d) a *response* to the situation that can entail changes in subjective experience, physiology, and/or facial or whole-body behavior (see Figure 1). For instance, an emotion of anxiety may arise when a person experiences or imagines a job interview (situation); pays attention to what could go wrong (attention); appraises the situation as threatening (appraisal); and feels anxious, starts to sweat, and wishes to flee (response).

The affective responses generated on one iteration of this feedback loop may become part of the situation stage of a subsequent iteration. For instance, the person may now realize that he is being interviewed while anxious and perspiring (situation), fixate on increased chances of failure (attention), appraise the situation as even more threatening (appraisal), and experience even stronger anxiety (response). Successive iterations of the affect generation loop can produce increasingly selective attention, elaborate appraisals, and specific responses.

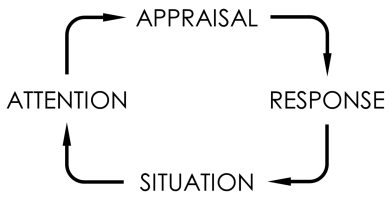

Figure 1 Affect generation. Different affective states such as emotions, stress responses, impulses and moods can be viewed as iterative cycles of attending to, appraising and responding to situations.

We suggest that the same four iterative stages are involved in different kinds of affective states, although the stages can differ in their automaticity, specificity, duration, and other features. One way to organize different affective states within this framework is to place them on a continuum based on how many affect generation stages are generally part of the conscious experience of the given affective state.

At one end of this continuum are emotions, where all four stages are generally part of the experience. Emotions such as anxiety or joy tend to involve strong feelings directed at a situation that commands attention and is at least in part consciously appraised[27,31].

At the other end of the continuum are moods such as depression or elation, that tend to be experienced as diffuse feelings and action tendencies (i.e., only the response stage). We argue that the remaining affect generation stages play a role in moods outside of conscious awareness. Thus, moods tend to relate to situations that have been selectively perceived and appraised largely outside of awareness[32,33].

Between emotions and moods in the continuum are stress responses and impulses. Stress responses, such as feeling threatened or feeling challenged[8,34], resemble emotions in that the attention, appraisal and response stages are usually part of the experience. However, instead of a single identifiable situation, these experiences revolve around broader circumstances, such as a divorce or a new job, that span several specific situations.

Impulses, such as an urge to flee or to have a drink, can be viewed as affective states experienced as a constellation of the response and the situation stages. Impulses can feel almost like reflexes – strong action tendencies (i.e., response stage) elicited by some threat or opportunity (i.e., situation stage)[17]. We argue that the intermediate stages of selectively perceiving and appraising the situation are often operative in impulses, albeit outside awareness.

The four-stage model of affect generation is a flexible way to appreciate both commonalities and differences among different kinds of affective states. Importantly for current purposes, the model also suggests that unhealthy affect can be traced back to maladaptive unfolding of one or more of the four affect generation stages. Sometimes, unhealthy affect arises simply due to a maladaptive situation, such as being a victim of violence. When unhealthy affect arises from otherwise adaptive situations, however, it may be because of maladaptive unfolding of attention, appraisal or response stages of affect generation. For instance, the mental health consequences of maladaptive attention are illustrated by the role of attention biases in mood and anxiety disorders[35,36]. The consequences of maladaptive appraisal are illustrated by the role of interpretation biases in people with

depressive symptoms[37]. The consequences of maladaptive affective responses are illustrated by the role of low physiological reactivity in externalizing syndromes such as sociopathy[38].

Maladaptive affect generation is therefore an important part of a comprehensive account of unhealthy affect. However, in this paper, our primary focus is affect regulation. This is because maladaptive affect generation manifests in unhealthy affect mostly when affect regulation fails to neutralize – or even further aggravates – the maladaptive affect.

AFFECT REGULATION

Affect regulation involves intentional (but not necessarily conscious) attempts to change the intensity, duration, frequency or type of current or anticipated affect[39]. We focus in this paper on self-generated or *intrinsic* affect regulation, which can be distinguished from other-generated or *extrinsic* affect regulation[40,41]. The latter – which involves one person's attempt to regulate the affective states of another person – is also important for mental health, but falls beyond the scope of this paper.

Mirroring the four kinds of affective states distinguished earlier, we may distinguish four kinds of affect regulation: a) emotion regulation[15,16,42]; b) regulation of stress, i.e. coping[8,43]; c) regulation of impulses, i.e. self-regulation[17,44]; and d) mood regulation[18,45]. Even though the type of affect targeted by regulation can be important to distinguish, our analysis of common mechanisms of affect generation suggests that there are also common mechanisms of affect regulation.

The process model of affect regulation highlights these shared mechanisms by addressing two fundamental questions: a) how can affect be regulated (strategies), and b) what processes underlie affect regulation (stages).

Affect regulation strategies

To understand how affect can be regulated, it is useful to return to the four stages of the affect generation loop outlined in Figure 1. Given the stages of situation, attention, appraisal and response, we can distinguish four families of affect regulation strategies, based on which affect generation stage they primarily influence (see Figure 2).

Situational strategies seek to alter affect generation at the situation stage, by selecting which situations are encountered (*situation selection*) or modifying what is going on in them (*situation modification*)[44]. For instance, people wishing to lift their depressed mood may call a friend (situation selection) or guide an already ongoing conversation to uplifting topics (situation modification).

Attentional strategies seek to alter affect generation at the attention stage, by changing what aspects of the situation are attended to[46]. For instance, the person experiencing depressed mood may distract himself from negative thoughts by diverting his attention to a game such as Tetris.

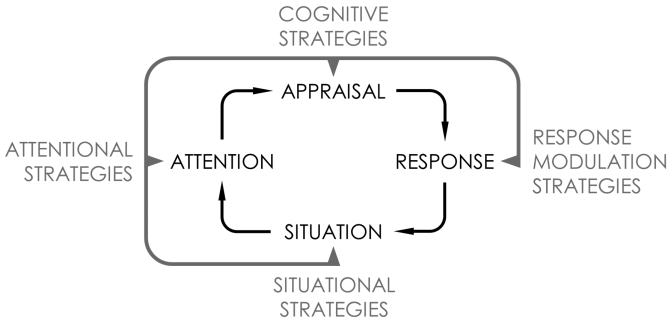

Figure 2 Affect regulation strategies. Four families of affect regulation strategies can be distinguished based on which stage of affect generation they primarily seek to alter.

Cognitive strategies seek to alter affect generation at the appraisal stage, by modifying how the situation is viewed in light of goals, values, and other motivational concerns[47]. For instance, depressed mood could be fought off by considering how things are not as bad as they initially seemed.

Finally, *response modulation strategies* seek to alter affect at the response stage, by counteracting the affect-related experiential, behavioral or physiological changes. For instance, the person experiencing depressed mood may prepare a cup of coffee to energize his body.

In addition to mood regulation, the same strategy families have been found to be relevant for regulating emotions[42], stress[22] as well as impulses[44,48].

Each of the four broad ways of changing affect can be effective, but each has different costs and benefits[49,50]. For instance, strategies that intervene early in the affect generation cycle can provide powerful relief from the affective state[51], but this may come at the cost of limited learning[52,53]. As researchers have identified different costs and benefits of regulation strategies, it has become clear that adaptive affect regulation requires matching strategies to the characteristics of the affect being regulated, the individual, and the current context[54-56]. For instance, in a context where a frustrating situation can be improved, it is sensible to try to change the situation rather than to use cognitive strategies to change how the situation is appraised. By contrast, in a context where nothing much could be done to improve the situation, it is sensible to use cognitive rather than situational strategies[57-59].

Affect regulation stages

If deciding how to best regulate affect appears such a complex task, how is it accomplished? The process model of affect regulation addresses this question by envisioning a series of four stages: identification, selection, implementation and monitoring (see Figure 3). Each stage can be thought of as a decision that the person makes, consciously or otherwise[60,61]. Returning to the example of the person experiencing depressed mood, what decisions does he need to make to regulate his mood?

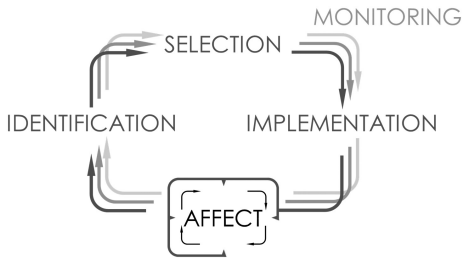

Figure 3 Affect regulation stages. Affect regulation consist of key decisions that people make, consciously or otherwise, during four stages. At the identification stage, people decide what, if anything, should change about affect. At the selection stage, they decide which affect regulation strategy to use in service of that goal. At the implementation stage, they decide which actions to take as part of the chosen strategy to alter the affect generation process. The monitoring stage consists of iterative updates to the identification, selection and implementation decisions that amounts to a separate decision about whether ongoing efforts should be maintained, switched or stopped.

First, at the *identification* stage, he needs to decide that his current mood should be improved. This decision then activates the *selection* stage, where he needs to decide which affect regulation strategy to use (i.e., where to intervene in the affect generation cycle). For instance, he may select an attentional strategy to keep his mind off ruminative thoughts. Strategy selection triggers the *implementation* stage, where the person needs to decide which specific actions to take. For instance, he may play a game of Tetris.

As the chosen actions intervene in affect generation, all three decisions may need to be updated – whether the affect continues to require regulation, whether an attentional strategy continues to be the best strategy, and whether playing Tetris continues to be the best course of action. The continued iteration of the three decisions can be thought of as a separate *monitoring* stage of affect regulation, where the person needs to decide whether to maintain, switch or stop the ongoing affect regulation attempt.

To better understand the identification, selection, implementation and monitoring stages, it is helpful to consider what information is processed to reach the decisions required at each stage. The process model of affect regulation suggests that each stage makes use of two main inputs, and we now turn to describing the role that these inputs play in each of the four stages.

The identification decision of what, if anything, should change about affect (i.e., what is the regulation goal) relies on: a) a representation of the current affective state together with alternative states, and b) the evaluation of the costs and benefits of these states in the given context.

The first input to the identification decision thus requires representing ongoing affective states together with other states that the person could experience in the given situation. The importance of this input is illustrated by the finding that people who are good at detecting and labelling their affective states tend to also be good at affect regulation[62,63].

The second input to the identification decision consists of the evaluation of the current and alternative affective states based on their costs and benefits. Most of the time, people evaluate affective states in light of the hedonic motive to increase pleasant feelings and decrease unpleasant feelings. However, people can also make counter-hedonic (i.e., instrumental) evaluations, for instance when they wish to be angrier than they currently are because they believe that this will help them negotiate[64].

When the identification stage is working well, the person detects the current affective state together with alternatives, evaluates them appropriately, and decides (consciously or otherwise) what, if anything, should change about the current affective state.

A decision to change affect triggers the *selection* stage, at which point the person decides where to intervene in affect generation (i.e., which regulation strategy to use). The selection decision relies on: a) a representation of available regulation strategies, and b) the evaluation of the costs and benefits of these strategies in the given context.

The availability of strategies can vary between situations as well as individuals. For instance, cognitive strategies are more likely to be considered in situations that have multiple interpretations[65]. Different individuals may consider different strategies based on their skills and abilities. For instance, attentional strategies work better for people with relatively high working memory capacity[66], suggesting that they are more likely to consider these strategies as a viable regulation option.

The second input to the selection decision is the evaluation of costs and benefits of available strategies[67]. One major benefit of each available strategy is its expected efficacy to change affect. For instance, when attempting to downregulate intense emotions, people tend to prefer distraction (an attentional strategy) over reappraisal (a cognitive strategy), because the former is believed to be more effective[67]. Some of the major costs include the time and effort needed to use the strategy[68]. Other costs and benefits, more specific to different strategies, individuals and contexts, also help to shape the eventual choice of strategy.

When the selection stage is working well, the person represents available strategies, evaluates them appropriately, and decides which regulation strategy to use.

The selection decision triggers the *implementation* stage, where the person decides how to enact the selected strategy in the given context. This stage is needed because the broad strategies of intervening at one of the four stages of affect generation can be enacted in different ways[69], sometimes referred to as regulation tactics. For instance, having made an identification decision to lift depressed mood, and a selection decision to rely on attentional strategies, the person may decide to play Tetris as a way to get his mind off his negative thoughts. Such an implementation decision relies on: a) a representation of different actions afforded by the situation, and b) the evaluation of the costs and benefits of these actions in the given context.

The implementation stage is where the regulation process reaches its target, as specific mental or physical actions impact the affect generation process (see Figure 3). For instance,

playing Tetris diverts cognitive resources away from the attention stage involved in generating depressed mood.

When the implementation stage is working well, the person represents actions afforded by the specific context, evaluates them appropriately, and decides how to enact the regulation attempt.

The identification, implementation and selection decisions form an iterative cycle. As the strategy *selected* to serve the *identified* regulation goal is *implemented*, each of these decisions may need to be updated to mirror changes in the regulated affect as well as in the broader context. Iterative updates to the affect regulation decisions can be viewed as a separate *monitoring* stage, involving a decision to either maintain, switch or stop the regulation attempt. Inputs to this decision include: a) changes in affect, which can be spontaneous as well as caused by ongoing regulation, and b) changes in context.

As long as the regulation attempt continues to produce desired changes to affect, and the context also does not change substantially, the person can *maintain* regulation by relying on the latest identification, selection and implementation decisions (e.g., play Tetris to fend off rumination in order to lift depressed mood). However, if affect resists change, or changes in undesired ways, the chosen implementation, strategy or regulation goal can be *switched*, or the regulation attempt can be *stopped* altogether. Switching or stopping may also be mandated by a change in context, such as when a friend calls in the middle of the Tetris game.

To be adaptive, affect regulation should respond with optimal flexibility to changes in affect as well as in context[43,55]. Not enough flexibility can lead to overuse of certain affect regulation behaviors, whereas too much flexibility can lead to lack of persistence.

When the monitoring stage is working well, the person appropriately represents ongoing changes in affect as well as in context, and decides to maintain, switch or stop regulation accordingly.

MALADAPTIVE AFFECT REGULATION AND MENTAL ILLNESS

The process model of affect regulation outlined in the previous sections can be helpful for considering how maladaptive affect regulation can contribute to mental illness. The identification, selection, implementation and monitoring decisions can be considered maladaptive when they are misaligned with the targeted affective state, the current motives of the person, and/or contextual demands[54-56]. In this section, we consider how each of these decisions can become maladaptive. We use selective examples of manifestations of mental illness such as different symptoms, syndromes and disorders. Note that, even when we discuss a particular mechanism in relation to a particular manifestation, we do not intend to imply that a given manifestation could not be related to other mechanisms nor that a given mechanism could not be involved in other manifestations of mental illness.

Identification difficulties

Unhealthy affect may arise from the identification stage of affect regulation when the decision of what, if anything, should change about an affective state is maladaptive. This can happen when a person encounters difficulty with at least one of the inputs to the identification decision, i.e., by misrepresenting affective states and/or misevaluating their costs and benefits.

The first kind of difficulty is characteristic of individuals high on trait alexithymia, who struggle to attend to and accurately identify their affective experiences[70]. Compared to healthy controls, these individuals have been found to engage in maladaptive affect regulation patterns[71] which may arise from the low granularity with which they represent affect. Alexithymia is also common among individuals with mental illnesses such as autism spectrum disorder[72] or eating disorders[73], suggesting that the unhealthy affect characterizing these mental illnesses may also arise in part from misrepresented affective states.

The second difficulty associated with the identification stage involves misevaluation of the costs and benefits of either the current affective state or alternative states that could be experienced. For example, people with panic disorder tend to overestimate the costs of current anxiety[74]. They may interpret a normal anxiety-related increase in heart rate as a sign of imminent heart failure, or anxiety-related thoughts as a sign of imminent loss of their grip on reality. Such overestimation of costs of affect can produce a maladaptive identification decision to launch an unnecessary regulation attempt. In addition to costs, people can also misestimate the benefits of affective states. For instance, individuals with bipolar disorder often choose not to downregulate maladaptive positive affect, even though they are able to do so when instructed[75]. One reason may be that individuals with bipolar disorder overvalue the hedonic benefits of positive affective states at the expense of the costs of these states as well as the benefits of alternative states[76].

Selection difficulties

Unhealthy affect may arise from the selection stage of affect regulation when the decision about which regulation strategy to use in order to accomplish the regulation goal is maladaptive. This can happen when a person encounters difficulty with at least one of the inputs to this decision, i.e., by misrepresenting available strategy options and/or misevaluating the costs and benefits of these strategies.

One reason for misrepresenting available strategies may be that the person has limited skills or experiences with different strategies. For instance, people with alcohol use disorder may struggle to consider strategies other than consuming alcohol, which they are most familiar with[77]. A similar limitation may characterize individuals suffering from binge eating disorder, who often engage in unhealthy eating patterns for affect regulatory purposes[78].

Another way the selection stage may contribute to unhealthy affect is via difficulties with evaluating the costs and benefits of different strategies. Many mental illnesses are associated with misevaluation of maladaptive regulation strategies. For example, engagement in non-suicidal self-injury relies in part on the evaluation of this costly behavior as an effective affect regulation strategy[79,80]. People with generalized anxiety disorder meanwhile view worry, another strategy with negative consequences, as productive (e.g., "Worrying helps me to be prepared and avoid adversities") or as an indicator of good character (e.g., "Worrying means that I care")[83].

Difficulties with the cost-benefit analysis of strategy options may also arise from more general decision biases. For instance, a broad range of mental illnesses are associated with amplified temporal discounting, whereby immediate outcomes are overvalued relative to long-term outcomes even more than in healthy populations[81]. Amplified discounting can bias affect regulation strategy selection towards underestimating long-term costs and benefits relative to short-term ones. For instance, people with social anxiety disorder tend to choose behavioral avoidance to reduce anxiety despite it severely restricting social or professional outlooks for the future[82].

Implementation difficulties

Unhealthy affect may arise from the implementation stage of affect regulation when the decision about how to enact the selected strategy in a given situation is maladaptive. This can happen when a person encounters difficulty with at least one of the inputs to this decision, i.e., by misrepresenting available affordances for action and/or misevaluating their costs and benefits.

The first difficulty may arise when a person fails to consider action affordances beyond obvious ones suggested by habit and the environment. For instance, someone looking for ways to implement a situational strategy for increasing excitement may fail to consider options beyond watching the TV that happens to be in the room. Detecting less obvious action affordances often requires cognitive control[84], a set of processes that tends to be impaired across a range of mental illnesses[85]. Cognitive control impairments are particularly relevant in attention-deficit/hyperactivity disorder (ADHD)[86], which is also characterized by maladaptive affect regulation[87]. Our analysis suggests that maladaptive affect regulation in ADHD may stem, among other pathways, from difficulties to detect less obvious regulation tactics.

Another difficulty encountered at the implementation stage is the misevaluation of costs and benefits of different action affordances. This suggests that mental illnesses that impair predictions about action outcomes, such as major depressive disorder[88,89], may contribute to maladaptive affect regulation by making it harder to appropriately evaluate action affordances even if they are detected. For instance, a person may come up with more ways than watching TV to implement an attentional strategy to feel more excited, but then fail to consider some of their outcomes, leading to a maladaptive choice. According to the present framework, one mechanism through which affect regulation becomes maladaptive in people with depressive symptoms[90] may therefore involve misevaluation of the action affordances that have been detected during the affect regulation process.

Monitoring difficulties

Unhealthy affect may arise from the monitoring stage of affect regulation, when the decision to maintain, switch or stop regulation is maladaptive. This can happen when the person encounters difficulties with at least one of the inputs to this decision, i.e., by misrepresenting changes to the regulated affect and/or to the relevant context. As the consequences of these difficulties are quite similar, we will not distinguish between them. Instead, we consider two directions of misrepresentations – under-representing changes in affect or context that contributes to insufficient regulation flexibility, and over-representing changes in affect or context that contributes to too high regulation flexibility[55].

Insufficient flexibility can lead to unnecessary maintenance of regulation efforts that have already succeeded or are unlikely to succeed. Such inertia in regulation has been observed for numerous mental illnesses. For example, people with generalized anxiety disorder continue to worry despite it elevating anxiety and being cognitively costly[91,92]. Similarly, people with major depressive disorder continue to ruminate despite it increasing rather than decreasing depressed mood[93].

At the other extreme, the monitoring decision can become overly flexible when changes in affect or context are overrepresented. This difficulty can manifest in premature switches between strategies and their implementation before they have had a chance to become effective, or premature stopping of regulation altogether[55]. For instance, borderline personality disorder is characterized both by frequent shifts in affective states[94] as well as high levels of impulsivity[95]. This suggests that one reason for the affective lability in individuals suffering from borderline personality disorder may be insufficient persistence in applying affect regulation, i.e. overly high affect regulation flexibility.

IMPLICATIONS FOR ASSESSMENT AND TREATMENT

Assessment and treatment of unhealthy affect is central to a number of psychotherapeutic approaches, including cognitive-behavioral therapy[96], dialectical-behavioral therapy[97], acceptance and mindfulness-based interventions[98-101], emotion-focused therapy[102], affect regulation training[103], and emotion regulation therapy[104]. The present framework complements these approaches by offering four broad insights that have implications for clinical assessment as well as treatment.

First, the framework suggests that problems with different affective states, such as emotions, stress responses, impulses and moods, can be analyzed in common terms. Second, unhealthy affect usually arises from some combination of maladaptive affect generation and maladaptive affect regulation. Third, maladaptive affect regulation can arise from identification, selection, implementation and monitoring decisions. Finally, affective processes are equally relevant for mental illness and psychological well-being. In this final section, we briefly discuss the assessment and treatment implications of each of these insights.

Common concepts for different affective states

Emotions, stress responses, impulses and moods have often been studied as separate phenomena, leading to separate assessment instruments and treatment approaches. Without denying instances where such distinctions are useful, the process model of affect regulation suggests that is also reasonable to focus on the similarities rather than differences between affective states.

The framework highlights the iterative stages of situation, attention, appraisal and response, and the ways to regulate them, as a set of concepts that are sufficiently broad to capture different affective states. For instance, take a problematic affect such as generalized anxiety, that is experienced as a diffuse feeling with variable awareness of the situation, attention and appraisal stages of affect generation. Working with a client reporting this affective pattern, a clinician may seek to reveal the contents of these antecedent stages[105]. What are the situational triggers for these states? Are there selective perceptual processes involved? How is the selectively perceived situation appraised? Even though the client may initially lack awareness of these stages, he may provide reliable information through interviewing techniques such as behavioral chain analysis[97]. Relevant information may also be obtained through daily assessment techniques that can recover aspects of situations and cognitions that tend to be less available at later recall[106].

Focusing on similarities between different affective states can also be useful for selecting and tailoring treatments for specific clients. For example, borrowing an insight from systematic desensitization[107], a therapist may develop a hierarchy of affective states based on how difficult they are for a client to regulate. For instance, a client may resist unhealthy food with ease, downregulate his anger with moderate success, but almost never overcome a bout of depressed mood. The therapist could incorporate this hierarchy into a program of guided affect regulation practice that introduces different regulation techniques using assignments from the lower end of the hierarchy and gradually moving upwards. For instance, a client could first foster healthier eating habits through situation modification by putting healthy snacks in easily accessible locations. He may then use this experience as a helpful metaphor for finding ways to use situation modification to improve his depressed mood.

Interplay of affect generation and regulation

The process model of affect regulation suggests that the same manifestation of unhealthy affect may arise from different mixtures of maladaptive affect generation and maladaptive affect regulation[2].

On the one hand, this suggests that affect generation and affect regulation form an integrated dynamic system that can be analyzed as a single functional unit. For instance, for many clinical purposes, such as initial screening for affective disturbances, it is largely unimportant whether a problematic affective pattern reflects overly strong affect generation or overly weak affect regulation. On the other hand, the process model also exemplifies the value of separating the contributions of affect generation and regulation to unhealthy affect. Teasing these contributions apart can be challenging, as the client may have limited awareness of the functioning of different affective processes. The interviewing techniques discussed above may be adapted to this task. In addition, the research community has started to devise promising combinations of self-report, behavioral and statistical approaches for separating affect generation from affect regulation[39].

Differentiating affect generation from affect regulation can also be important for designing targeted treatments. In many cases, people suffer from a combination of maladaptive affect generation and maladaptive affect regulation, and thus benefit from simultaneous – or sensibly sequenced – treatments targeting both. For instance, in the case of major depressive disorder, pharmacological interventions can be used to treat maladaptive affect generation, while psychotherapy can be used to improve affect regulation[108]. Omitting one or the other component from the treatment regime would reduce its overall efficacy. There can also be cases where the unhealthy affective pattern can be traced back to a single primary source among affect generation and affect regulation processes. In these instances, adequate targeting of treatment becomes even more important. For instance, consider a client who is already relatively proficient in affect regulation but suffers primarily from maladaptive affect generation. If offered only further affect regulation training, with no help with maladaptive generation, he might experience reduced self-efficacy that could lead to deterioration of the therapeutic relationship and treatment compliance.

Decomposing affect regulation

The third implication of the process model of affect regulation is that the stages of identification, selection, implementation and monitoring, and their respective inputs, can be used as more specific targets for assessment as well as treatment.

For instance, an assessment approach could be designed to determine difficulties with *identifying* regulation goals, *selecting* regulation strategies, *implementing* them through contextually suitable actions, and *monitoring* the outcomes to make necessary modifications. Parts of these phenomena

can be assessed using existing self-report instruments, such as the Toronto Alexithymia Scale[109], the Emotion Regulation Questionnaire[110], the Cognitive Emotion Regulation Questionnaire[111], the Difficulties in Emotion Regulation Scale[112], the Coping Flexibility Scale[113], and many others. However, as these measures assess overlapping but incomplete aspects of the four affect regulation stages, we encourage future efforts to design comprehensive measures of the process model of affect regulation. These efforts may extend beyond self-reports to behavioral and psychophysiological assessments such as measuring affective responses to standardized stimuli using physiological correlates under specific instructions[114].

Clarifying whether a particular affect regulation problem arises from difficulties during the identification, selection, implementation or monitoring stage can be an important step toward making informed decisions about personalized treatment options. For instance, people who exhibit difficulties during the identification stage due to misrepresentation of current affective states might benefit from mindfulness-based therapy modules and technological aids. People who exhibit difficulties during the selection stage might benefit from learning new adaptive strategies, from increasing strategy specific self-efficacy, as well as from modification of dysfunctional beliefs contributing to misevaluation of strategies. People who struggle with the implementation stage might benefit from external aids such as mobile applications with suggestions on how to execute different strategies. People who struggle with the monitoring stage might benefit from mindfulness interventions to increase awareness about changes in the affective state and context as well as training to switch between strategies according to changing circumstances. In most cases, individual clients may exhibit difficulties with more than one, but not necessarily all, decisions involved in affect regulation.

From mental illness to well-being

Although this paper has focused primarily on mental illness, the process model of affect regulation is equally relevant when considering the role of affect in psychological well-being[115]. The goals of psychiatry and clinical psychology extend from preventing and reversing maladaptive affect generation and regulation patterns to promoting and restoring their adaptive counterparts. To live up to this ideal, assessment as well as treatment approaches should be designed without forgetting about healthy affect. For instance, assessment approaches should target affective states that are known to improve well-being. These include hedonically positive experiences such as satisfaction, happiness or love, as well as affective states that can be hedonically negative but still add eudaimonic value by providing meaning, elevating experiences, or fostering personal growth[116].

Psychological well-being is equally relevant for designing interventions. We have seen how the process model of affect regulation can be used to organize regulation techniques aimed at reducing hedonically negative (e.g., depressed mood) and instrumentally harmful affective states (e.g., maladaptive positive affect in bipolar disorder). However, the process model is an equally useful framework for organizing techniques that promote hedonically positive or instrumentally helpful affective states. For instance, situational strategies such as going for hike can be used to generate pleasant mood[117]. Attentional strategies such as focusing on things that a person is grateful for can be used to promote happiness and a sense of meaning[118]. Cognitive strategies such as contrasting a mental image of a job well done with the current situation where more work is needed can be used to promote feeling challenged and thereby more motivated[119]. Response modulation strategies such as exercising can be used to generate feelings of being relaxed and fulfilled[120]. Promoting each of these behaviors can further benefit from analyzing their antecedents within the identification, selection, implementation and monitoring stages.

CONCLUSIONS

We have proposed a process model of affect regulation as a common framework for understanding how affect is generated, how it can be regulated, and how both processes jointly contribute to mental health. This framework conceives of affect generation as a four-stage feedback loop, and affect regulation as a coordinated four-stage decision process. Adaptive functioning of each of these stages promotes mental health and well-being, whereas maladaptive functioning of these stages can increase the risk of mental illness.

We believe that the process model of affect regulation offers a useful framework for clinical research as well as practice. The model is in line with broader efforts to reveal the transdiagnostic dimensions underlying mental illnesses[14,121]. It relates complex affective patterns to simple psychological mechanisms such as feedback loops[29] and decision processes[122,123], which are amenable for computational and neural research.

The model calls for more research, in particular to realize the assessment and treatment avenues it opens up. On the one hand, it is important to provide further evidence that different symptoms, syndromes and disorders are indeed linked to difficulties in different affect generation and affect regulation stages. On the other hand, it is also important to clarify how existing treatments impact these stages as well as to devise novel treatments.

We hope that, by facilitating and scaffolding these important advances, the process model of affect regulation can contribute to the advancement of evidence-based personalized psychiatry and psychotherapy.

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Creating headspace for integrated youth mental health care

International momentum in global mental health reform is building, responding to overwhelming evidence of unmet need in high, middle and low income countries alike, and powerful economic arguments that mental health care represents the best value for money. Yet adequate investment remains an elusive goal, with the treatment gap as wide as ever[1].

We have long argued that new paradigms that dispel stigma, open up early access, safeguard hope, and build expertise and quality based on the best available evidence, must be embraced and scaled up in real world settings[2]. The growing success of prototypical evidence-based early psychosis models in many parts of the world has paved the way for a more definitive reform paradigm, one which links transdiagnostic early intervention with a decisive focus on young people.

Early intervention to reduce the impact of potentially serious mental and substance use disorders is an achievable goal if we focus on the period of peak risk of onset. Young people aged between 10 and 24 years make up over a quarter of the world's population, and mental ill-health is their key health issue and leading cause of disability. Virtually all major mental and substance use disorders emerge during the transitional zone between puberty and mature adulthood but, despite being burdened by the highest incidence and prevalence of adult type mental disorders, young people have the worst access to health care. Society as a whole and health systems in particular have comprehensively failed our young people, and at a time when their mental health appears to be deteriorating. This paradox is finally beginning to be recognized, and progressive jurisdictions around the world are designing and scaling up novel youth and family friendly systems of care to address this serious public health problem[2].

"Integrated youth health care" is an enhanced primary care model offering "soft entry" to care with access barriers minimized. It provides a high capacity first step in stepped or staged care, with other pathways able to flow from this initial low stigma source. It is highly consistent with the global strategy long advocated by the World Health Organization, namely to build and blend mental health expertise within primary care platforms.

The key features are:

- Youth (and family) participation and co-design at all levels, enabling youth-friendly, stigma-free cultures of care providing what young people and their families really need.
- Developmental appropriateness reflecting the epidemiology of mental ill-health and providing a good cultural fit for adolescents and emerging adults aged 12-25 years.
- Integration of mental health, physical health, alcohol and other drug, and vocational support.
- An optimistic early intervention approach offering safe, holistic, evidence-informed, proportional and stage-linked care, including risk-benefit considerations and shared decision-making, with social and vocational outcomes as the key targets.
- A single, visible trusted location, a "one stop shop" or "integrated practice unit"[3] with providers organized as a dedicated team of clinical and non-clinical (e.g., peer worker) personnel providing the full spectrum of care around the young person and his/her family.
- Elimination of discontinuities at peak periods of need for care during developmental transitions, in particular demolishing the anachronistic and developmentally inappropriate "hard border" at age 18.
- Seamless linkages with services for younger children and adults.

Reform began in Australia in 2006, with Australian government funding for ten headspace centres[4]. They have been scaled up through a series of funding rounds, reaching a total of 110 centres in early 2019. Centres are commissioned through a lead agency and local consortia, and have rapidly gained strong local community and political support from all sides and levels of politics. To June 2018, 446,645 young people accessed headspace centres, phone or online (eheadspace) services, with 2.5 million occasions of service delivered. In 2017-8, 88,500 young people accessed face-to-face headspace centre services, and 33,700 accessed online or via phone. headspace also offers suicide postvention services in high schools, and vocational recovery interventions online and face to face. Six early psychosis platforms linked to clusters of local headspace portals build on the primary care model with comprehensive evidence-based care for early psychosis in community settings.

Independent evaluation of headspace centres confirmed that they provide much better access to young people, with very high levels of satisfaction and safety[5]. Outcome studies show that 60% of young people improve significantly either symptomatically, functionally or both[6,7].

Despite this tangible success, which has inspired similar models internationally, headspace remains a work in progress. It offers mostly brief episodes of care, and the effect size for improvement in the total sample remains small to modest compared to usual (poorly accessed) care. There are several reasons for this. First, headspace is a treatment delivery system and offers the same treatment content as usual care, albeit more efficiently and in a single location. Second, capped funding and the lack of funding streams for key pillars, notably alcohol and other drug and vocational interventions, mean that tenure of care and model fidelity need to be strengthened. Third, outcomes for the large subset of more complex and unwell young people, whose needs can only be met by more intensive expert services, obscure the benefits for those with earlier presentations who are most likely to do well with this model by not progressing to more severe or persistent illness and functional impairment.

headspace currently only provides access to a minority of the young Australians who need it. At least 132 centres could be

justified on cost-effectiveness alone, with many more required for full national coverage[5].

Each region of Australia needs a cluster of headspace entry-level portals seamlessly linked to transdiagnostic specialized care integrating mental and physical health with alcohol and other drugs expertise, vocational interventions and online/digital health platforms. Assertive and intensive home-based care, and clinicians with expertise in complex syndromes (such as borderline, eating, mood and psychotic disorders) are missing elements, and interface with hospital-based services is therefore needed. Strong national oversight to assure integrative commissioning, stronger financial models, additional funding streams, longer tenure and greater depth of expertise will strengthen the capacity of the model.

The youth mental health paradigm is in its infancy and will be driven by a dynamic blend of grassroots and professional leadership[8]. Early adopters, inspiring leaders, philanthropic visionaries and patrons have emerged in progressive regions of the world, notably Ireland, Canada, Denmark, Israel, the Netherlands, France, Singapore, and parts of England and California[9]. Child and adolescent psychiatry, still a seriously undersized speciality, has begun to recognize the need and opportunity for a paradigm shift, which it has labelled "transitional psychiatry". Momentum within and beyond the mental health field is building and could be decisive in paving the way for a wider revolution in mental health care.

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Recovery colleges as a mental health innovation

There is a consensus among the mental health community that recovery from mental illness involves much more than symptom remission. Indeed, people with mental illness often define recovery in terms of living a meaningful, autonomous and empowered life in the community[1]. Yet they continue to experience numerous inequalities, including high rates of unemployment, low rates of educational attainment, considerable public stigma and social exclusion.

Recovery colleges are a new initiative aimed at people with mental illness to support their recovery and address these inequalities. The first recovery colleges emerged in the US in the 1990s, informing a model that has been adapted and implemented across the world in the last decade[1]. In 2009, the first recovery college opened in London, and there are now more than 70 in the UK[2]. Recovery colleges now exist in over 20 countries, including Hong Kong, Italy, Sri Lanka, Israel, Japan and the Netherlands. Moreover, a recovery college international community of practice has been established to promote research, knowledge exchange and understanding.

Some descriptive research has examined the defining characteristics, core values and central features of recovery colleges. These are mostly single-site case studies[3,4], which have been compared for shared themes in two recent systematic literature reviews[5,6]. These studies indicate several common core characteristics across recovery colleges.

First, recovery colleges tend to be based on the theory and practice of adult education, rather than clinical or therapeutic models[3]. As such, they possess many of the core characteristics of an adult education college: registration, enrollment, term curricula, full-time staff, sessional teachers and a yearly cycle of classes. Attendees are students (not patients, clients or service users), and they strive to be serious places of learning[2]. As such, some colleges are physically located in mainstream adult education institutes (e.g., Mayo Recovery College, Ireland) or higher education settings (e.g., Boston University Recovery Education Program).

Second, they offer a range of educational courses that individual students can tailor to their own specific circumstances. These courses often focus on equipping students with new skills that can foster various aspects of their (broadly defined) recovery[5,6]. This can include courses on health related factors such as illness management, self-care and physical health; as well as courses on life skills, employment and information technology[2,4,7].

Third, recovery colleges are characterized by the meaningful involvement of people in recovery (peers) in all aspects of college life[3-5]. Peers are often employed as course teachers, either alone or in conjunction with other experts. This is known as co-delivery. Peers are also frequently involved in college governance and management, with strong input into decisions about curriculum, structure, staffing and overall philosophy. This collaboration between professionals and peers is known as co-production. The emphasis on co-delivery and co-production makes recovery colleges distinct from traditional educational practice.

Recovery colleges receive operating funds from a variety of organizations, including official health services, non-profit and corporate donations; as well as government employment and education departments[2,7]. The existing descriptive literature

indicates that the physical location of recovery colleges differs considerably[2,6]. Some are in the community (e.g., Calgary Recovery College, Canada), while others are within hospitals and mental health services (e.g., Butabika Recovery College, Uganda). New models are also emerging, such as online recovery colleges (e.g., https://lms.recoverycollegeonline.co.uk/). Given this variation, research comparing different funding and service delivery models is needed.

Current evidence indicates that recovery colleges are popular with students, and that college experience can be beneficial to recovery[6,7]. Furthermore, colleges can engage people who find existing services unappealing, and are associated with self-reported improvements in several domains, including self-esteem, self-understanding and self-confidence. Futhermore, students have reported a positive impact on occupational, social and service use outcomes.

Indeed, recovery colleges have the potential to equip students with new skills that can help their entry into the workforce[5,6], but there is little quantitative research examining specific impact on employment outcomes. Interestingly, a recent empirical study indicates that colleges may have beneficial impacts beyond the student, by positively affecting the attitudes of mental health staff, reducing stigma within health and social service systems, and increasing inclusiveness in wider society[9].

Research and evaluation examining recovery colleges is expanding, with ongoing studies in Canada, England and elsewhere. That said, most existing research has uncontrolled, single-case or retrospective designs. There is a lack of rigorous quantitative research and there has not been any randomized trial. Nonetheless, this situation is rapidly changing. A recent rigorous study used a controlled before-and-after design to analyze mental health service use in a large sample of recovery college students, finding that students had lower rates of service utilization after attending a college[8].

Similarly, a 39-college UK study developed and psychometrically validated recovery college implementation checklists and a fidelity scale (available at researchintorecovery.com/recollect) to assess modifiable and non-modifiable components[5]. This study confirmed that an educational approach and the use of co-production are foundational to recovery colleges. Importantly, most research has occurred in high-income anglophone countries such as the UK, US, Canada and Australia, indicating a need for further research elsewhere.

In summary, recovery colleges are a tangible manifestation of the international push to make the mental health system more recovery-oriented[1]. They are a pioneering intervention that enact much of the theory and evidence surrounding recovery. First, they can help students address functional and educational deficits that contribute to high rates of social exclusion. Second, they can equip students with self-care techniques, encouraging them to successfully manage their illness and take control of their life[2]. Third, they are based on an effective partnership between experts by experience (peers) and experts by training (clinicians)[3]. Hence, recovery colleges have the potential to foster individual student recovery, as well as catalyze wider service change and reduce societal stigma[6,9].

In conclusion, recovery colleges offer something very different from current pharmacological and psychological interventions. They have enthusiastic proponents, but rigorous evidence about their impact on outcomes is missing. In particular, randomized controlled trials are needed which evaluate their impact on social and functional outcomes, as much as clinical and service use outcomes.

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Mental Health First Aid training: lessons learned from the global spread of a community education program

Many health education interventions achieve limited dissemination, even when there is supporting evidence for their efficacy[1]. We think there are lessons to be learned for those aiming to disseminate such interventions from those rare examples where the dissemination has been successful. Here we describe the factors that appear to underlie the success of one such program: Mental Health First Aid (MHFA) training.

The MHFA training program conducts courses which teach members of the public how to provide mental health first aid, which has been defined as "the help offered to a person developing a mental health problem, experiencing a worsening of an existing mental health problem or in a mental health crisis; the first aid is given until appropriate professional help is received or until the crisis resolves"[2]. Participants are trained to: approach, assess and assist with any crisis; listen and communicate non-judgmentally; give support and information; encourage appropriate professional help; encourage other supports.

MHFA training began in Australia in 2000 as a collaboration between one volunteer with lived experience of mental illness (BAK) and a researcher (AFJ)[3]. From this small beginning, it spread rapidly in Australia and to other countries. By mid 2018, over 700,000 Australians had been trained and the program had spread to 25 other countries, with over 2.7 million people trained globally[4].

We believe that six factors underlie this successful dissemination.

The first is that MHFA training builds on the familiar First Aid model. Members of the public are familiar with the idea that they can help in a physical health emergency if professional help is not available, and many people have done a First Aid course. It is a natural extension to expand this concept to include mental health problems.

The second factor is that MHFA training fulfills a public need. Because the prevalence of mental disorders is so high, members of the public will frequently have contact with people who are affected[5]. Many people lack knowledge and confidence in how to help, which may motivate them to seek training.

The third factor is that the course has been tailored to meet different needs. In addition to the standard MHFA course for adults to assist other adults, courses in Australia have been tailored for specific age groups (e.g., adults helping youth, adults helping older people, teenagers helping their peers), professional roles (e.g., medical and nursing students, legal professionals) and cultural groups (e.g., indigenous people, people from non-English speaking background)[6]. When MHFA training is disseminated in other (mainly high-income) countries, there is tailoring to local languages, health systems and cultures, including for minority groups.

The fourth factor is that there is a strong partnership with research. The content of MHFA training has been based on expert consensus guidelines developed using Delphi studies[7]. The experts in these studies have been mental health professionals and people with lived experience. The guidelines have covered how to assist with a wide range of developing mental health problems and crises. The Delphi method has also been used to draw on cultural expertise in assisting people from special groups (e.g., indigenous Australians; refugees and immigrants; lesbian, gay, bisexual and transgender people).

The other area in which research has been important is evaluation of outcomes. From the very first MHFA courses taught, evaluation data were gathered and published[8]. These data have now expanded considerably, with 18 controlled trials in a range of countries. A systematic review and meta-analysis of these trials showed improvements in mental health first aid knowledge, recognition of mental disorders, beliefs about treatments, confidence in helping, intentions to help and amount of help actually provided[9]. MHFA training also leads to a reduction in stigma[9].

The fifth factor is that dissemination is devolved rather than centralized. In Australia, MHFA training is run by Mental Health First Aid International. This organization trains instructors but does not employ them. Rather, the instructors are employed by non-governmental organizations (NGOs), government agencies or private businesses. This devolution has allowed well-targeted local marketing by instructors. When MHFA training is disseminated in other countries, there is a partnership with a local organization, generally a mental health NGO or a government agency. Again, the decentralized dissemination facilitates roll-out by drawing on local knowledge in a way that a centralized model would not.

The sixth factor is that there is a sustainable funding model. In Australia, government and philanthropic grants have been used for development, initial dissemination and evaluation of new training products, but such grants are time limited and not a sustainable basis for ongoing funding. However, like First Aid, MHFA training is potentially sustainable by offering courses on a fee-for-service basis. A longer-term aim is for MHFA training to become accepted as a necessary qualification for certain human services roles, as is the case for physical First Aid training, which will facilitate sustainability.

In recent years, MHFA International has received many enquiries about local training from low- and middle-income countries. However, major health system and cultural differences between these countries and Australia, where the program originated, mean that the appropriateness of course content and implementation models in these settings is unknown. In general, evidence in low- and middle-income countries on how best to translate, adapt and scale-up population mental health interventions that have shown benefit in high-income countries is limited.

In 2017, in collaboration with investigators from China and Sri Lanka, we were awarded a Global Alliance for Chronic Diseases grant to develop and trial MHFA training for these countries. This project represents the first effort to formally adapt MHFA training to lower-resource countries. We have recently started a similar program of work in collaboration with researchers in Brazil, Chile and Argentina. These projects offer opportunities to identify and evaluate the most appropriate models for cultural adaptation and implementation of community-based education programs that aim to improve population health.

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Nidotherapy: a cost-effective systematic environmental intervention

The notion of nidotherapy is a familiar one in mental health, although the word itself may be unusual to many. The familiarity derives from the awareness that the environment is important in both helping and hindering recovery from mental illness. The added component of nidotherapy is that it describes the systematic and collaborative manipulation of the environment to carry out this task[1]. The word is derived from the Latin *nidus*, or nest, as a bird's nest is ideally placed to accommodate whatever object is placed within it. It also carries with it the connotations of comfort and homeliness, encapsulated in the German word *gemütligkeit*, which has no good equivalent in English.

The practice of nidotherapy involves manoeuvring all aspects of the environment to make a better fit between the person and setting[2]. In this context all aspects of the environment – physical, social and personal – become relevant. This wide range is necessary as, to put it in its most literal sense, feeling at home in yourself encapsulates all three of these environments. The adjectives "systematic" and "collaborative" are highly relevant here as, although health professionals may think of, and often use, environmental changes in the course of helping people, they rarely do this in a coherent jointly planned way.

Nidotherapy in a minor form is practised by all. We choose our occupations, our places to live, our sexual partners, and our leisure activities, and in so doing we are clearly manipulating our environment. These choices are too straightforward to be regarded as therapy, but for many with severe mental illness environmental options are much more limited, and in the most extreme examples are not obviously present at all. In professional nidotherapy practice, the environmental problems that are presented are not straightforward. They are best described as puzzles, as they represent a set of complex interacting problems that require close scrutiny and analysis before solution.

Many of them come under the heading of desired but resisted environmental changes (DRECs) as opposed to other changes[3]. This is where the skills of nidotherapy come into play. When there is resistance to a feasible change that is wanted by both therapist and patient, this can be created by the patient, those close to the patient, the system in which the patient is placed, or by excessive concern over risk. The last of these is a very frequent block to change in those with severe mental illness, as the patient's wish for greater autonomy collides with concern about potential dangers.

The practice of nidotherapy is relatively straightforward in principle, but can provoke challenges in practice. It has four components: the development of a therapeutic relationship, so allowing a good understanding of wishes and needs; environmental analysis involving physical, social and personal environments; the establishment of a plan for change (the nidopathway); and subsequent monitoring of the pathway[2]. The challenges include the difficulties of getting good relationships with people who feel they have been persistently let down, the logistical problems of effecting suitable change when others block it for manifold reasons, and the need for flexibility if the original environmental plan is thwarted.

The collaborative element is very important. The role of the nidotherapist is to act as a guide for the patient, not a leader or director of change. The environmental decisions are made by the patient and owned accordingly. This is of particular relevance when problems arise in the nidopathway. If the patient is committed to make the change work, he/she is more likely to overcome difficulties that hinder implementation, as cognitive dissonance will then always err on the side of the planned nidopathway.

Who should practise nidotherapy is an easier question to answer. In practice we have found that, although experienced practitioners may be needed to help in choosing the time of treatment and the changes needed, other professionals, especially those at the coalface of care, are better able to implement the changes. In this respect, carers are often ideally placed to ensure that changes are adhered to and motivation maintained[2]. One of the assets of nidotherapy is that coalface practitioners can be found in all countries and do not require additional financial investment, so one consequence is that nidotherapy is very cost-effective[4].

Many disorders can be treated by nidotherapy, and it can be described as a transdiagnostic treatment. In general, it is reasonable to consider nidotherapy when a problem is either not amenable to known evidence-based therapies (e.g., intellectual disability, most personality disorders)[5-7] or has failed to respond to such treatments, for which the most evidence is in schizophrenia[8].

Most practitioners recognize that many chronic disorders persist because they are embedded in toxic situations. But, at this point, they all too frequently accept these situations as impossible to change, and indulge in what can be only called passive palliative therapy: "You have to accept the place you are in; we can support you as much as possible until things improve". This is not an acceptable answer if change is feasible, which is the case more often than not.

Currently the evidence base for environmental interventions is fairly limited. This seems to be due to a paradoxical combination of complexity (there are so many possible environmental changes and their interactions that you cannot accommodate all of them), and simplicity (all environmental changes are straightforward and require no special skills). So, a wide-ranging group of environmental interventions in forensic mental health – from therapeutic communities, programmes to enable environments, and what has become known as social prescribing[9] – have remained the province of qualitative research and only rarely have received formal evaluation.

Social prescribing is the most recent of these, and is currently being promoted in some countries, including the National Health Service in England, as an aid to primary care. The idea is simple. Expensive health professionals with limited time to

help with common problems, including prevention as well as treatment, can be assisted by others incurring lower costs in giving advice and support. In some areas social prescribing specialists have also been appointed.

Nidotherapy is informed, systematic and sophisticated social prescribing. As such, it deserves a place in all mental health services.

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Further information on nidotherapy, including training, can be found at www.nidotherapy.com.

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Nonsocial and social cognition in schizophrenia: current evidence and future directions

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Cognitive impairment in schizophrenia involves a broad array of nonsocial and social cognitive domains. It is a core feature of the illness, and one with substantial implications for treatment and prognosis. Our understanding of the causes, consequences and interventions for cognitive impairment in schizophrenia has grown substantially in recent years. Here we review a range of topics, including: a) the types of nonsocial cognitive, social cognitive, and perceptual deficits in schizophrenia; b) how deficits in schizophrenia are similar or different from those in other disorders; c) cognitive impairments in the prodromal period and over the lifespan in schizophrenia; d) neuroimaging of the neural substrates of nonsocial and social cognition, and e) relationships of nonsocial and social cognition to functional outcome. The paper also reviews the considerable efforts that have been directed to improve cognitive impairments in schizophrenia through novel psychopharmacology, cognitive remediation, social cognitive training, and alternative approaches. In the final section, we consider areas that are emerging and have the potential to provide future insights, including the interface of motivation and cognition, the influence of childhood adversity, metacognition, the role of neuroinflammation, computational modelling, the application of remote digital technology, and novel methods to evaluate brain network organization. The study of cognitive impairment has provided a way to approach, examine and comprehend a wide range of features of schizophrenia, and it may ultimately affect how we define and diagnose this complex disorder.

Key words: Schizophrenia, cognition, social cognition, cognitive neuroscience, social neuroscience, functional outcome, cognitive enhancement, cognitive remediation, metacognition, computational modelling, childhood adversity, brain network organization

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The study of cognition has substantial implications for understanding neural systems, treatment and prognosis in schizophrenia. It has been a major research focus for a long time. How long? That depends.

It can be argued that cognition has been a focus for schizophrenia research over 100 years, since the insightful observations of Bleuler, Kraepelin and early phenomenologists[1-3]. It can also be said that it has been a focus since the infusion of experimental psychology into schizophrenia studies following World War II[4-6]. Or, it has been a major focus since cognitive neuroscience and the associated neuroimaging methods opened up non-invasive ways to examine brain functioning in schizophrenia[7-9]. Or when its relevance for daily functioning was realized and documented[10-12]. Or when it started to become a focus of pharmacological and cognitive remediation treatments[13-16]. Or, perhaps, the focus is finally emerging now with the development of a wealth of novel concepts and methods.

This paper considers two branches of cognition: nonsocial and social. Nonsocial cognition includes the more commonly considered mental abilities, such as attention/vigilance, working memory, learning and memory, speed of processing, and reasoning and problem solving[17,18]. It can also include auditory and visual perceptual processes[18,19]. Social cognition refers to psychological processes involved with the perception, encoding, storage, retrieval and regulation of information about other people and ourselves[20-23].

We first summarize knowledge about some aspects of cognition in schizophrenia that are longstanding and well-established. We then provide a status report on the relevant cognitive domains, the neural substrates of cognition, the connections to community integration, and the variety of treatment approaches designed to improve cognition in schizophrenia. In the last section, we present a selection of topics that have emerged only in recent years.

NATURE OF NONSOCIAL AND SOCIAL COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

Cognitive domains relevant to schizophrenia research

Research on cognition encompasses a broad range of processes involved in perceiving, processing and generating responses to stimuli in the physical and social environment to achieve goals and function adaptively during the course of daily life.

It is now very clear that schizophrenia is associated with wide ranging cognitive impairments. As summarized in Table 1, the breadth of impairment spans from basic perceptual processes to complex nonsocial and social cognitive processes. The table also provides examples of daily life functioning tasks that are associated with each of these processes. Here we summarize the types of cognitive and perceptual deficits that are typically assessed with performance-based cognitive tasks used in schizophrenia research.

Nonsocial cognition

Schizophrenia research has predominantly focused on nonsocial cognition (also referred to as neurocognition). Scores of studies document that nonsocial cognitive impairments are pervasive, substantial and fundamental illness features. Impairments are seen across a range of domains, assessed through computerized or pencil-and-paper tasks, most

Table 1 Relevant perceptual, nonsocial cognitive, and social cognitive domains in schizophrenia

Domain	Description of process	Real-world example
Perception		
Visual	Using the visual system to perceive and interpret what is seen in the surrounding environment	Identifying structural visual features in faces or objects
Auditory	Using the auditory system to perceive and interpret what is heard in the surrounding environment	Distinguishing between the tone or pitch of voices
Nonsocial cognition		
Speed of processing	Responding quickly and accurately when performing relatively simple perceptual, motor or cognitive tasks	Being able to rapidly add up a set of numbers or count out change
Verbal learning and memory	Ability to acquire, store and retrieve verbal information for more than a few minutes	Remembering a list of items to purchase at the supermarket, or remembering what you read hours ago
Visuospatial learning and memory	Ability to acquire, store and retrieve information about objects and spatial locations for more than a few minutes	Remembering where you placed something in a closet
Working memory	Ability to hold and manipulate information "online" in a temporary store	Retaining and dialing a phone number you were just told
Attention/Vigilance	Ability to respond to targets, and not respond to non-targets, over a period of time	Focusing attention while receiving instructions or reading a book
Reasoning and problem solving	Ability to apply and shift strategies effectively to find optimal solutions to problems	Figuring out how to get to an important appointment when your car breaks down
Social cognition		
Emotion processing	Ability to effectively identify emotions (e.g., facial expression) in others and to manage one's own emotions	Being able to identify from your boss' face whether he/she is angry at you
Social perception	Ability to identify social roles, rules and context from non-verbal cues including body language, prosody and social schema knowledge	Figuring out the relationship between two people based on a brief sample of conversation
Attributional bias/style	The way in which individuals explain the causes and make sense of social events or interactions	Jumping to the conclusion that you are in danger when you feel fearful
Mentalizing	Ability to represent the mental states of others and make inferences about their intentions and beliefs	Being able to take another person's perspective during a conversation

commonly including speed of processing, verbal learning and memory, visuospatial learning and memory, working memory, attention/vigilance, and reasoning and problem solving[24].

Speed of processing refers to the ability to perform cognitive operations, typically involving relatively simple perceptual and motor tasks, quickly and efficiently. Verbal learning and memory refers to the initial encoding and subsequent recall and recognition of words and other abstractions (e.g., stories, word pairs) involving language. Visuospatial learning and memory similarly involves the initial encoding and subsequent recall and recognition of non-verbal information such as color, shape, movement and location. Working memory involves temporarily holding, or holding and manipulating, information online, typically over a relatively brief period (e.g., several seconds); it can be assessed with either verbal or visual stimuli. Attention/vigilance refers to sustained concentration over prolonged periods of time, which is required to direct and focus cognitive activity on specific stimuli. Finally, reasoning and problem solving refers to a set of cognitive processes involved in logical and strategic thinking, generating and initiating plans, and behavioral monitoring to flexibly solve problems and attain goals. These domains are rather broad, and specific subprocesses within them, such as cognitive control within reasoning and problem solving, are often the focus of particular studies in schizophrenia.

All of these domains, when assessed reliably, reveal notable differences between schizophrenia and healthy comparison groups. Across domains, people with schizophrenia typically show impairments ranging between 0.75 and 1.5 standard deviations from healthy samples[25,26]. In the context of pervasive impairment on these types of tasks, particularly marked deficits are often found for the domains of long-term memory and speed of processing.

Several converging lines of evidence support the conceptualization of nonsocial cognitive impairments as core features of the illness[27-29]. Nonsocial cognitive impairments are largely independent of positive psychotic symptoms, cannot be explained by antipsychotic medications or their side effects, are present at comparable levels at the time of illness onset, are relatively stable over time until late life, and are detectable at attenuated levels in unaffected biological relatives of patients and in prodromal samples (i.e., samples considered to be at high risk for psychosis). The evidence that nonsocial cognitive impairments reflect a primary deficit associated

with vulnerability to schizophrenia is thus strong and compelling.

Social cognition

Interest in social cognition as it relates to schizophrenia is a more recent development, and research in this area has grown dramatically over the past 10-15 years. Social cognition is a very broad area that encompasses the mental operations needed to perceive, interpret and process information for adaptive social interactions. The most commonly studied aspects of social cognition in schizophrenia include emotion processing and mentalizing. A considerably smaller number of studies have examined the areas of social perception and attributional bias.

Emotion processing refers broadly to perceiving and using (e.g., regulating) emotions adaptively, with facial emotion perception/identification being the most frequently studied aspect in this area. Mentalizing refers to the ability to infer the intentions, dispositions, emotions and beliefs of others, including whether they are being sincere, sarcastic or deceptive. Over 50 studies consistently document large impairments in emotional perception/processing (d=0.89) and mentalizing (d=0.96)[30] in people with schizophrenia.

Social perception assesses an individual's ability to identify social roles, social rules, and social contexts from non-verbal cues (e.g., voice intonation, body language, proxemics). A small number of studies indicate a large impairment in this area (n=12; d=1.04)[30] in people with schizophrenia.

Attributional bias refers to how different individuals typically infer the causes of particular positive and negative events, such as having an increased tendency to attribute hostile intentions to others in ambiguous social situations. Unlike the other social cognitive areas, results across the smaller number of studies of attributional bias are mixed as to whether those with schizophrenia do or do not show significant differences from healthy individuals[30,31].

Similar to nonsocial cognition, there is growing evidence that emotion processing, mentalizing, and social perception impairments are core features of schizophrenia that are present at a comparable level in recent-onset patients, not secondary to positive symptoms or medication effects, relatively stable over the course of illness, and detectable at attenuated levels in unaffected biological relatives of patients and in prodromal or other high-risk samples[32,33].

Perceptual impairment in schizophrenia

Perception can be considered the initial step in cognition. One can regard cognition as a cascade of processing events beginning with early perception and leading in steps to higher mental processes. If the perception information is degraded, the subsequent steps will be affected. Although less studied than higher-level nonsocial cognitive abilities (such as memory, problem solving, and attention), people with schizophrenia also experience a range of perceptual deficits, including problems in processing auditory and visual stimuli[19,34]. Many experimental paradigms have been used to explore early visual and auditory processing impairment in schizophrenia. Here we briefly describe one from each sensory modality.

The visual masking paradigm is one way to probe early visual processing with excellent temporal precision[35]. In this paradigm, a visual target is followed or preceded by a "mask" that can either completely overlap or surround the target. When the mask follows the target, it is called backward masking; when the mask precedes the target, it is called forward masking. Data from numerous laboratories consistently show impairment in schizophrenia during backward masking compared to healthy controls[36-38]. Visual perceptual impairments assessed with visual masking paradigms in schizophrenia are related to both social and nonsocial cognition[39,40], consistent with a cascade model of cognition.

Auditory information processing deficits have been consistently identified in patients with chronic, recent-onset, and unmedicated schizophrenia, and in individuals at high clinical risk for developing psychosis (i.e., prodromal)[34,41-43]. One commonly used early auditory assessment index is mismatch negativity (MMN), which is an event-related potential elicited in response to infrequent, deviant tones interspersed in the repeated presentation of a standard tone[44]. MMN is thought to reflect automatic, preattentive information processing, as it can be elicited without directing attention to stimuli[44]. It tends to correlate with measures of nonsocial cognition[41,45], social cognition[46], and functional outcome[47,48].

Cognitive impairment in schizophrenia vs. other disorders

Considerable work has been conducted to compare the magnitude and pattern of cognitive impairment of schizophrenia to other disorders. In terms of comparisons with neurological disorders, schizophrenia patients showed a distinctly different pattern of cognitive impairments from those with dementia – for example, memory retention (i.e., holding on to information that is already learned, as opposed to how long it took to learn the material in the first place) is markedly impaired in Alzheimer's disease, but intact in schizophrenia[49,50]. The distinctive patterns of cognitive impairment between schizophrenia and dementia indicate that different underlying mechanisms are at work.

The pattern of cognitive impairments in schizophrenia has also been compared with other psychiatric disorders, such as bipolar disorder. One meta-analysis[51] found that schizophrenia patients were impaired, compared with healthy controls, on premorbid nonsocial cognitive function with an effect size of approximately 1.30, whereas bipolar patients showed an effect size of 0.6. A similar pattern was also found in a meta-analysis on first-episode patients with bipolar disorder or schizophrenia[52]. Schizophrenia patients also showed impairment on multiple social cognitive domains compared to both controls (effect sizes 0.88-1.04)[30] and patients with bipolar disorder (effect sizes 0.39-0.57)[53]. Notably, patients

with mood disorders who have a history of psychosis appear to show impairments that are comparable to those of schizophrenia patients on some cognitive domains (e.g., attention, working memory), but not others (i.e., speed of processing)[54]. Thus, schizophrenia patients show greater impairment compared to patients with bipolar disorder on both nonsocial and social cognition.

Recently, a few studies have compared social cognitive impairments in schizophrenia to those in autism, yielding mixed findings. Specifically, some studies found comparable impairments between individuals with schizophrenia and adults with autism on facial affect recognition and mentalizing[55,56]. However, others reported that schizophrenia patients showed poorer performance on an auditory affect recognition task, but better performance on a mentalizing task, compared to adults with autism[57,58]. Given a paucity of comparisons on nonsocial cognition, it remains to be determined whether these two disorders show distinct patterns of impairment across social and nonsocial domains.

Cognitive impairment across phases of illness and across lifespan

A large literature has examined cognitive impairment across phases of schizophrenia. Several meta-analyses showed cognitive impairments among individuals who are at clinical high risk for psychosis[33,59], who experience their first episode of psychosis[60], or who have chronic schizophrenia[61]. Among individuals at clinical high risk for psychosis, those who later developed psychosis did not differ from those who did not on several domains of nonsocial cognition[62].

These findings raise at least two intriguing questions. The first is whether cognitive impairments change over the course of illness (e.g., decline or improve as clinical symptoms change). Longitudinal studies with patients who recently experienced psychotic episodes showed that performance on cognitive tasks remained stable over time. For example, levels of nonsocial cognitive impairment at the onset of psychotic symptoms were similar to those at 2-year or 10-year follow-up assessment[63]. Similarly, performance of first-episode schizophrenia patients on social cognitive tasks was stable over five years[64]. However, some studies suggest that older schizophrenia patients (e.g., over 65 years old) show worsening nonsocial cognitive performance[65,66].

The second question is whether cognitive impairments are present even before clinical manifestations start emerging (i.e., in the premorbid period). Findings from population-based studies largely support premorbid deficits in nonsocial cognition in schizophrenia. For example, individuals who later developed schizophrenia showed impaired cognition even before age 10[67,68]. Subjects who later developed schizophrenia also showed increasing deficits in cognition over time, especially during adolescence[69,70]. It remains to be determined whether individuals who develop schizophrenia also show premorbid deficits in social cognition.

FUNCTIONAL NEUROIMAGING AND COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

During the past two decades, a remarkable amount of work has been done to characterize the neural bases of cognitive impairment in schizophrenia, using diverse neuroimaging and electrophysiological methods.

We briefly focus here on findings from studies using functional magnetic resonance imaging (fMRI), as this is the primary method used to explore regional specificity and neural circuits related to cognitive impairment in schizophrenia. Rather than trying to summarize the very extensive available literature, we describe the types of approaches that have been used.

Regional activation patterns and cognitive impairment

Earlier work using fMRI focused on regional activation associated with a specific cognitive function. Overall, this line of work demonstrated that schizophrenia patients show abnormal fMRI activations in key regions compared to healthy controls during cognitive tasks.

If we use working memory as an example, schizophrenia patients showed less fMRI activation in the dorsolateral prefrontal cortex and posterior parietal cortex[71-73], although the exact pattern of fMRI activations in these regions may vary based on task characteristics[74,75]. During long-term memory tasks, schizophrenia patients showed reduced fMRI activation in the medial temporal regions, including hippocampus, and dorsolateral and ventrolateral prefrontal cortex[76,77]. During a visual perception task, schizophrenia patients showed reduced fMRI activation in the lateral occipital complex[78,79].

In addition to these findings of reduced activation during cognitive tasks, there are sometimes reports of hyperactivation in schizophrenia. When hyperactivation is observed in brain regions that are normally activated for that specific cognitive function (e.g., hyperactivation in the dorsolateral prefrontal cortex during working memory[80,81]), they are often attributed to inefficient recruitment of neural resources. In contrast, studies that have found hyperactivation in regions different from those typically involved in a given cognitive task[82] are viewed as evidence of compensatory processes in schizophrenia.

Fewer studies have examined the neural bases of social cognitive impairment in schizophrenia, but emerging evidence indicates aberrant neural activations in this domain as well. For example, meta-analytic reviews of fMRI studies on facial affect recognition[83,84] have showed hypofunction in key social brain regions, including amygdala and fusiform gyrus, and hyperactivation in brain regions that are not typically associated with facial affect recognition, such as parietal lobule and superior temporal sulcus.

Similarly, aberrant neural activation has been observed during mentalizing[85]. Schizophrenia patients showed hypoactivation in several areas related to mentalizing, including medial prefrontal cortex, posterior temporoparietal junction and ventromedial prefrontal cortex, as well

as hyperactivation in the dorsal section of temporoparietal junction.

Less work has been done on an integrative social cognitive process such as empathy (i.e., sharing, understanding and responding to the emotional experiences of another person)[86-88]. During cognitive empathy (same as mentalizing) tasks, schizophrenia patients showed reduced fMRI activation in several key regions, including medial prefrontal cortex and precuneus[89,90], whereas normal neural activation was observed during tasks of affective empathy (also called affect sharing)[91,92].

Functional connectivity and cognitive impairment

Researchers are increasingly examining the connections between regions and neural networks that subserve cognitive processes[80]. During working memory tasks, schizophrenia patients showed several forms of reduced connectivity compared with controls: between prefrontal cortex and parietal cortex[93,94], between thalamus and the frontoparietal regions[95], and between prefrontal cortex and basal ganglia[96]. Also, during episodic memory tasks, schizophrenia patients showed reduced connectivity between hippocampus and frontal regions[97,98].

Similarly, studies on social cognitive impairment suggested that the associated neural circuits are disrupted. For example, compared to controls, schizophrenia patients showed reduced functional connectivity involving the limbic structures (including amygdala) during facial affect processing[99,100]. During a mentalizing task, schizophrenia patients showed reduced connectivity between temporoparietal junction and temporal lobe regions (including hippocampus and middle temporal gyrus) compared to controls[101].

While connectivity studies are informative regarding the ways and degree to which regions interact, the field is now moving to more sophisticated studies of network organization and graph theory methods that can examine how large sets of nodes communicate (see below the section on "Brain network organization").

IMPLICATIONS OF COGNITIVE IMPAIRMENT FOR COMMUNITY INTEGRATION

The introduction of antipsychotic medications in the 1950s was a game changer in schizophrenia treatment and outcome[102], but its impact was more narrow than first anticipated. Medications reduced psychotic symptoms in the majority of people with schizophrenia, and it was expected that such improvement would be accompanied by enhanced community integration. That did not happen. Unfortunately, the introduction of antipsychotics had little impact on functional outcomes[103,104]. It took some time to appreciate the key difference between remission (i.e., symptom reduction) and recovery (i.e., full participation in social, work, and independent activities), which depends on other factors, including cognition.

There is a very substantial literature on the relation between cognitive impairment and functional outcome in schizophrenia. For example, a PubMed search with the terms "schizophrenia", "cognition" and "functioning" yields over 200 published articles on this topic each year from 2011 to 2017.

Nonsocial cognition and functional outcome

All of the earlier reviews focused on nonsocial cognition[10-12,105]. The reviews demonstrated that cognitive impairment has reliable relationships to functional outcomes in schizophrenia. These outcomes included community-based functioning (e.g., work success, independent living) or ability to acquire skills in rehabilitation programs for inpatient samples. The consistency of the relationships was impressive, but the strengths of the associations were typically in the medium range (e.g., r=0.3) when considering individual cognitive domains. The relationships were generally stronger (r=0.5 or greater) when multiple cognitive domains were combined into composite scores[11].

This association between nonsocial cognition and outcome has been replicated in many countries, in different languages, with different types of cognitive assessments, and in different patient groups. Further, it has been found across different phases of illness, including the prodromal phase[106] and the first episode[107]. The relationships are present in prospective as well as in cross-sectional studies, indicating that cognitive impairment is a legitimate predictor of later community functioning. For example, several studies have found significant associations with outcome as long as 2-4 years after baseline assessment[108-111].

Social cognition and functional outcome

Following the established connections between nonsocial cognition and functional outcome in schizophrenia, the question turned to the associations between social cognition and outcomes. It soon became apparent that these latter associations were at least as large, and often larger, than those observed for nonsocial cognition[112,113].

Medium to large associations between social cognitive domains and community functioning were reported, with mentalizing showing the strongest relationship in a meta-analysis[113]. This meta-analysis reported that social cognition explained roughly 16% of the variance in community functioning, while nonsocial cognition accounted for about 6%.

The association between social cognition and functioning has been found to hold up over time. For example, significant associations between baseline social cognition and community functioning can be seen one year[107] and even five years[64] later.

Pathways from nonsocial and social cognition to functioning

The current question is no longer *whether* but *how* cognition is related to functional outcome. Considering the highly complex nature of community functioning in schizophrenia or any other condition, it is clear that many of the observed relationships between cognition

and community integration involve mediating variables. The identification of such key mediators is very important, because it can suggest specific therapeutic targets. If we identified a key mediator of functional outcome, this would become a rational target for intervention, especially because it would be considered to be closer (i.e., more proximal) to the eventual outcome of interest.

An initial series of studies evaluated whether aspects of social cognition (e.g., emotion perception and social perception) act as mediators between nonsocial cognitive processes and functional daily outcomes – demonstrated by significantly reducing or eliminating the direct relationship between nonsocial cognition and outcome. The results were consistent: in these models, social cognition acts as a mediator for functional outcome[39,114,115], with approximately 25% of the variance in functional outcome being explained by such mediation models[115].

These models are limited in the amount of explanation they can provide. Multistep models with several intervening variables can be more informative about the pathway(s) to functional outcome in schizophrenia. However, these latter models require more sophisticated analyses, such as structural equation modelling, and are difficult to test unless one has a sufficient number of variables, a large sample size, and a reasonable theory as to how the variables are expected to interact.

Beyond social cognition, additional intervening variables between nonsocial cognition and functional outcome include defeatist beliefs (i.e., an individual holds generalized negative beliefs about his/her ability to successfully perform tasks[116,117]) and motivational factors[118,119]. A study from our group using structural equation modelling found support for a single pathway from early visual perception (measured with visual backward masking) to functional outcome through social cognition, defeatist beliefs, and motivational negative symptoms[120]. The results indicated that cognition and motivation can be represented on a single pathway.

A more complex pattern of relationships emerged from a large multisite US study that examined the pathways from early auditory processing (including MMN and other early event-related potentials) to functional outcome[121]. Unlike the previous modelling study, this investigation did not include measures of social cognition or defeatist beliefs. The final model showed an indirect pathway from cognition through negative symptoms as well as a separate pathway from motivational/experiential negative symptoms to functioning. That is, a single pathway from cognition to motivation to functioning did not fully explain the data, perhaps because defeatist beliefs were not included in the model.

A third example comes from a large Italian multisite study that found multiple indirect pathways between nonsocial cognition and functioning. Social cognition and negative symptoms were important, but so were other factors such as internalized stigma, resilience, and engagement with services[122].

Overall, these complex modelling studies are extremely valuable in suggesting and testing mechanisms by which perception and cognition can lead to functioning through a series of intervening variables. However, the key question as to whether cognitive variables and motivational variables form single versus multiple pathways remains unresolved.

INTERVENTIONS FOR COGNITIVE IMPAIRMENTS

Over the past decade, there has been a great deal of excitement about developing new treatments that target nonsocial and social cognitive impairments as a means to improving functional outcomes in schizophrenia.

For nonsocial cognition, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative by the US National Institute of Mental Health (NIMH) spawned major efforts to discover new pharmacological approaches. There was also an extensive body of research on cognitive remediation interventions. Overall, the results have been mixed.

Social cognition has been a more recent topic of treatment development research. Efforts have predominantly focused on psychosocial training approaches, which are encouraging, with only a few studies considering pharmacological strategies.

Beyond these main treatment approaches, we also consider emerging evidence that alternative interventions, such as physical exercise and neurostimulation, may prove useful as adjuncts for enhancing cognition.

Nonsocial cognition

Pharmacological approaches

A wide range of candidate mechanisms involving diverse neurotransmitter systems have been proposed for pharmacological enhancement of nonsocial cognition[123]. The majority of studies have focused on glutamatergic and cholinergic agents, with fewer targeting other neurotransmitters, such as serotonin, dopamine, GABA and noradrenaline.

Despite considerable efforts across dozens of studies, these agents have not been consistently successful in improving cognition and functioning. Overall, a recent meta-analysis[124] reported that across all available studies (n=93) there was a significant, though quite small (Hedges' g=0.10), effect for overall cognition, with no significant effects for any cognitive subdomain.

For particular neurotransmitter systems, the literature is characterized by a lack of replication, and only a few agents have shown any evidence of positive benefits. The strongest findings were for agents acting predominantly on the glutamatergic system (overall cognition: g=0.19, n=29; working memory: g=0.13, n=20). Sub-analyses of particular glutamatergic agents indicated a significant small-to-medium benefit for AMPA receptor agonists on working memory (g=0.28; n=5) and a non-significant trend for memantine/amantadine on overall cognition (g=0.34; n=6). There were very few findings for other neurotransmitter systems: cholinesterase inhibitors showed a small yet significant effect on working memory

(g=0.26; n=6), and dopaminergic agents showed a non-significant effect on the domain of reasoning (g=0.34; n=4).

Despite several positive phase II studies showing cognition enhancement, these findings have not been replicated in larger phase III studies. Thus, the field is still struggling to find pharmacological interventions for cognitive enhancement in schizophrenia that show efficacy in multisite trials.

Cognitive remediation

Compared to pharmacological approaches, psychosocial interventions for cognitive remediation have produced more encouraging findings. A wide range of cognitive remediation approaches have used computerized or non-computerized (paper-and-pencil) training exercises with titrated increases in difficulty as participants progress through what is typically several months of fairly intensive treatment.

Cognitive remediation interventions can be classified along two broad dimensions: therapeutic target and therapeutic modality[125]. The therapeutic target can range from basic perceptual skills using a "bottom-up" approach (training on lower-level sensory processing to impact neuroplastic processes which are thought to generalize to higher-level cognitive and functional outcomes) to higher-level cognitive skills using a "top-down" approach (assuming that improvements will generalize to lower level and community functioning). The therapeutic modality can range from self-directed administration of cognitive training exercises with minimal therapist involvement to integrated cognitive training exercises with additional strategy monitoring, bridging, or other psychosocial treatments.

A meta-analysis of 40 studies demonstrated that, regardless of treatment target or modality, cognitive remediation shows significant, moderate gains in terms of near-transfer to untrained cognitive tests (d=0.45 for global cognition)[126]. Further, these gains were durable at follow-up assessments following active treatment (d=0.43). Notably, beyond cognitive task improvement, there is emerging evidence that cognitive remediation is also associated with significant structural (both grey and white matter) and functional (particularly in prefrontal and thalamic regions) brain changes[127].

Importantly, however, treatment modality is a key mediator of generalization to improvements in community functioning. Specifically, the effect of cognitive remediation is moderate when combined with adjunctive psychiatric rehabilitation (d=0.60), but only small and marginally significant when cognitive training is provided alone (d=0.19-0.29)[128]. Thus, while cognitive remediation generally yields moderate gains on cognitive task performance, it may be necessary to administer additional interventions (e.g., vocational rehabilitation, strategic bridging, or skills training) in order to achieve meaningful real-world functional benefits.

Emerging approaches

There is clearly ample room for improvement in the treatment of nonsocial impairment in schizophrenia. Efforts to develop new medications have been disappointing so far. Although there has been more progress for integrated cognitive remediation approaches at the group level, there is substantial individual variability in treatment response and many patients exhibit little benefit. One possible path forward is to examine whether the impact of integrated cognitive remediation is boosted when combined with pharmacological therapies. This is an active area of investigation, though preliminary findings have been mixed[129].

Another possibility that has opened up in recent years involves the use of novel non-pharmacological augmentation approaches intended to promote neuroplasticity, such as physical exercise and neurostimulation. A recent meta-analysis has shown that physical exercise can improve cognition in schizophrenia compared to non-aerobic control activities[130]. These encouraging findings have led to a few small pilot studies which found that the combination of cognitive remediation plus aerobic exercise leads to differential improvement for some aspects of cognition and functioning[131]. Similarly, based on findings that transcranial direct current stimulation (tDCS) may improve selected aspects of cognition in schizophrenia, a few small pilot studies have reported differential benefits of brief cognitive remediation plus tDCS (versus sham) interventions on trained cognitive tasks[131,132].

Social cognition

Training approaches

Over the past decade, there has been considerable progress in the development of psychosocial treatments for social cognition in schizophrenia. Initial proof-of-concept trials demonstrated that brief "targeted" interventions focusing on a single social cognitive domain (e.g., affect perception) led to significant task improvements[133,134]. Given the complex, multifaceted nature of social interactions and the wide range of social functioning difficulties seen in schizophrenia, the field has shifted toward "comprehensive treatments" that address multiple, rather than single, social cognitive domains. These are typically interactive, group-based treatments that incorporate a range of visual, auditory, video stimuli depicting social stimuli, though other formats, such as individual computerized interventions, have also been developed[135].

The results to date provide several reasons for optimism. A recent meta-analysis of 16 studies[136], conducted in diverse cultural settings, reported medium-to-large improvements in the two most commonly assessed domains: facial affect identification (d=0.84 in 12 studies) and mentalizing (d=0.70 in 13 studies). Effect sizes were also large for a smaller number of studies assessing social perception (d=1.29 in four studies) and small-to-medium for attributional bias (d=0.30-0.52 in seven studies).

Notably, treatment-related gains in social cognition are not accompanied by

improvements in nonsocial cognition[136], suggesting that social cognitive changes are independent of changes in nonsocial cognition. Consistent with this notion, nonsocial cognitive remediation alone does not result in significant social cognitive improvements[128]. Beyond improvements in social cognitive task performance, preliminary evidence also indicates that social cognitive interventions produce detectable structural and functional brain changes[137].

While these findings are quite encouraging, this is a relatively young area of research, and several factors should be considered[138]. First, most studies included small samples (<20), methodological quality varied considerably, and the durability of treatment effects is largely unknown. Second, there is currently no consensus in the field about an optimal set of social cognition outcome measures for clinical trials. Third, the generalizability of treatment benefits to meaningful improvements in daily life functioning has not yet been consistently demonstrated.

Thus, several open questions remain. For example, it is unclear which type of social cognitive treatment (e.g., group-based vs. individualized computer-based) is optimal, or whether treatment formats can be better matched to the personal characteristics of participants.

Emerging approaches

The few efforts to develop pharmacological approaches to social cognition in schizophrenia have focused on oxytocin. Building on extensive basic and clinical evidence that this neuropeptide enhances the salience of social information[139-141], a number of studies have examined the impact of intranasal oxytocin, using single or repeated administration strategies, on social cognitive tasks. Results have been mixed. A recent meta-analysis of 12 studies that randomized participants to oxytocin vs. placebo found no overall effect for social cognitive measures, although there was some suggestion (from a very small number of studies) of a significant (albeit small, d=0.20) effect for higher level (e.g., mentalizing) but not lower level social cognitive tasks[142].

Two studies evaluated oxytocin augmentation during the course of social cognitive training programs, using very different strategies, and yielded mixed findings. Our group administered oxytocin (vs. placebo) only prior to each training session, and found differential improvement in one aspect of empathy (how well someone can track momentary changes in mood in another person, referred to as empathic accuracy)[143], whereas the other study used twice-daily chronic dosing throughout treatment and found no social cognitive benefits[144].

Aside from oxytocin, studies have started to examine the possibility of improving social cognition in schizophrenia through physical exercise and neurostimulation with tDCS. Only a few studies have examined the effects of exercise, providing early encouraging results (g=0.71, based on three studies)[131]. An initial study by our team found that a single session of tDCS (vs. sham), administered over the prefrontal cortex, significantly improved facial identification task performance, though not other social cognitive domains[145]. However, a subsequent tDCS study using two stimulation sessions over the prefrontal cortex did not show any social cognitive benefits[146].

To summarize, oxytocin and tDCS appear to be safe, well-tolerated potential adjuncts to psychosocial interventions, though it remains to be determined how they can be optimally administered (e.g., which dosing to use[147]) to boost social cognitive training effects.

RECENT DEVELOPMENTS AND FUTURE DIRECTIONS FOR RESEARCH ON COGNITION IN SCHIZOPHRENIA

In this section we look to what lies on the horizon for research into cognition in schizophrenia. The topics are, by necessity, selective, and we could have chosen others. In the first part, we discuss lines of research that are growing and already have a reasonably large data base to support them. In the second, we discuss areas that are just getting off the ground, but have potential to substantially change our understanding of cognition in schizophrenia.

Recent areas of growing interest

The interface of motivation with cognition

There has been considerable research interest in how cognitive processes interface with disturbances in motivation and emotion in schizophrenia. Translational research based on developments in affective neuroscience has focused on how disturbances in reward-related information processing relate to diminished engagement in goal-directed behavior. Much of this work builds on the consistent finding that immediate hedonic responses to rewarding or pleasurable stimuli are largely intact in schizophrenia[148-150], indicating that motivational disturbances do not simply reflect a diminished capacity to experience pleasure. Instead, people with schizophrenia seem to have difficulty using reward-related information to adaptively guide future behavior. This has led schizophrenia researchers to develop and test multicomponent models of the computational processes through which reward-related information is translated into productive goal-directed activity[151,152].

Individuals with schizophrenia show impairments in several reward processing subcomponents that involve applying cognitive operations to rewarding stimuli. These include disturbances in long-term memory for rewarding/pleasurable experiences[153,154], reward learning and prediction error processing[155-157], the representation and maintenance of reward value within working memory[158], decision making concerning effort costs associated with obtaining rewards[159], and anticipation/prospection for future rewards[160,161]. Impairments in these areas are often, though not always, related to clinical ratings of motivational negative symptoms (e.g., anhedonia, asociality).

Along these lines, recent research has identified disturbances at the interface of

emotion and cognitive control processes. For example, in contrast to healthy individuals, reward incentives fail to enhance performance and associated neural activation (particularly of dorsolateral prefrontal cortex) during cognitive control tasks in schizophrenia[162-164], which has been described as impaired "motivated cognitive control". This failure to energize cognitive control processes required to formulate and execute goal-directed action plans has also been linked to motivational negative symptoms.

The impact of cognitive control disturbances also extends to processing negative emotional stimuli in schizophrenia. For example, people with schizophrenia show a diminished ability to downregulate their responses to unpleasant stimuli using effortful emotional regulation strategies such as cognitive reappraisal or directed attention[165-167]. Relatedly, they demonstrate an impaired ability to appropriately modulate or filter out negative distractor stimuli during tasks involving cognitive control (e.g., working memory, attention)[168,169]. Again, these control disturbances have often, but not always, been linked to negative symptoms or poor functioning.

Overall, there is growing evidence of widespread disintegration between cognitive and motivational/emotional processes in schizophrenia, which appears to have important clinical and functional implications.

Childhood adversity and cognition

Childhood adversity – such as physical and/or emotional neglect/abuse, poverty, malnutrition, traumatic experience – can have long-lasting negative consequences. It affects the development of the brain, such that individuals show both structural[170,171] and functional[172] cerebral abnormalities during adulthood. Because childhood adversity is also associated with increased risk for developing severe mental illnesses, including schizophrenia[173,174], it has been suggested that it could contribute to features of this disorder, including cognitive impairment.

Several studies examined the effect of childhood adversity on cognition in schizophrenia, primarily focusing on nonsocial cognition, and the findings have been mixed. A recent meta-analysis found a small effect of childhood adversity on cognition in schizophrenia, and this was significantly smaller than that seen in controls[175]. However, this meta-analysis examined only studies of nonsocial cognition, and did not explore whether different types of adversity or the timing of adversity (e.g., neglect vs. trauma, early vs. late childhood) has differential effects on cognition in schizophrenia. Notably, findings from recent studies suggest that social cognitive impairment is more related to neglect than other types of adversity[176,177].

Further, the mechanism through which childhood adversity may influence cognition in schizophrenia (e.g., neuroinflammation, neural changes), or any factors that may modulate this mechanism (e.g., gender, genetic or epigenetic processes), remain largely unknown[178-180].

Metacognition

Metacognition has received notable interest in both clinical and treatment development research on schizophrenia. Since the term was first used in the context of psychosis in the 1980s, to describe thoughts about one's own thoughts in a model of psychotic symptom formation[181,182], the definitions of metacognition have varied considerably, with some being quite broad. As an example of a broad definition, Lysaker and colleagues[183,184] propose that metacognition refers to a range of activities ranging from discrete (i.e., creating an idea about a specific thought or emotion) to highly synthetic (i.e., forming separate thoughts into complex representations of oneself and others). From this perspective, metacognition allows people to "access a sense of themselves (and of others) which is multifaceted and multidimensional, while also allowing for that sense of self and others to change responsively and adaptively as contexts change"[183].

Dozens of studies now document impairments in metacognition in individuals with, or at risk for, schizophrenia using discrete (based primarily on self-report questionnaires) or expansive (based primarily on clinical ratings of narratives) definitions[183,185,186]. Further, indexes of metacognitive impairment show associations with a wide array of clinical features, including positive, negative and disorganized symptoms, social and nonsocial cognition, motivation, self-agency, insight, and functional outcomes[183,185,187,188].

The varying definitions of metacognition make it challenging to provide an integrative summary of findings in this area. For example, the more expansive definitions of metacognition appear to have considerable overlap with other areas considered in the present paper, including aspects of social cognition (e.g., mentalizing, empathy) and nonsocial cognition (e.g., cognitive control, performance monitoring). While it can be argued that these are separable constructs[189,190], the extent of overlap among them is debatable.

Similarly, there are currently at least four different psychotherapies for schizophrenia that all include the term "metacognition" in their titles[191], as well as metacognitively-oriented cognitive remediation and social skills training[192,193]. Yet, these programs look rather different. Indeed, this has led to a debate in the schizophrenia literature about what constitutes a "true" metacognitive treatment[184,194,195]. Hence, fundamental questions remain about the scope and boundaries of this construct, and how it can be most productively distinguished from other areas of schizophrenia research.

Nascent areas with potential impact

Neuroinflammation and cognition

Accumulating evidence indicates the presence of an abnormal immune system in schizophrenia. For example, epidemiological studies have reported an association between maternal infection during pregnancy and increased risk for schizophrenia[196,197]. Also, a meta-analysis showed an association between schizophrenia and autoimmune disorders[198]. Recent evidence from genetic studies

indicates that schizophrenia-related loci include several genes involved in the immune system[199]. Patients appear to show elevated levels of peripheral inflammation markers[200] and increased activation of the central immune system[201].

Only a few studies so far have examined the associations between inflammation and cognitive impairment in schizophrenia. Most have focused on peripheral markers of inflammation, and the results have been mixed. For example, patients with elevated levels of peripheral inflammation markers showed poorer cognitive performance than patients with lower levels of inflammation[202]. A study of first-episode psychotic patients found that higher levels of inflammation were associated with greater cognitive impairment[203], whereas another study found the opposite pattern[204].

The associations between inflammation and cognition may differ across subgroups of patients. For instance, inflammation was associated with cognitive impairment only in patients who did not use illicit substances or alcohol[205], or only when patients were experiencing acute psychotic symptoms[206].

Thus, while a limited number of studies generally support the notion that inflammation is related to cognitive impairment in schizophrenia, the nature and strength of this association is still unclear.

Computational modelling of cognitive processes

Computational psychiatry is an emerging field that employs interdisciplinary tools from computational neuroscience, including machine learning algorithms, to address complex problems such as the classification of subgroups and characterization of cognitive impairment[207-209].

Computational psychiatry includes both data-driven and theory-driven approaches. Data-driven approaches have not been directed at probing cognitive impairment in schizophrenia as yet. Theory-driven approaches employ mathematical models to understand at a deep level cognitive impairments in schizophrenia. For example, one biophysically-based model focused on cortical microcircuits and working memory impairment in schizophrenia[210,211], suggesting that disturbed excitatory-inhibition balance due to disrupted glutamatergic signaling could explain working memory deficits. Another model suggested that reduced GABAergic activity in the visual cortex and disturbed connection between lateral geniculate nucleus and visual cortex contribute to visual perceptual abnormalities in schizophrenia[212]. Yet another approach focused on processes derived from a specific neural computing process (i.e., reinforcement learning) to explore latent processes that could contribute to impaired performance of patients during reinforcement learning tasks[156,213]. Finally, predictive coding (i.e., based on Bayesian inferences) is a neurocomputational process that may help to explain perceptual abnormalities of schizophrenia patients (e.g., MMN, motion perception)[214,215].

Hence, computational psychiatry is an emerging field that may provide valuable insights into the underlying mechanisms of cognitive impairments in schizophrenia.

Cognition and remote digital technology

There is now considerable interest in conducting cognitive assessments remotely on mobile devices. However, the benefits of this type of assessment are unclear. It has not been established that frequent, very brief, cognitive assessments of uncertain reliability are more valuable than fewer, longer assessments with demonstrated reliability. Further, there are benefits to having a tester in the room with a participant to monitor focus and effort of the testing session, something that is not possible with remote assessment. On the other hand, there would be advantages if participants can take tests from their home computers (as opposed to their smartphones), because the testing parameters and visual display could approximate those that occur in a testing lab. This arrangement would save the participant from coming into the lab, but would still not provide an ability to monitor the degree of engagement with the tests.

It is important to keep in mind the difference between two forms of digital data collection: active and passive. This distinction was not relevant until the arrival of smartphones. Active data collection is anything that involves intentional responses on the part of the participant, such as filling out an ecological momentary assessment survey of what they are doing or how they are feeling. Passive data collection, on the other hand, does not require actions from participants. These include using the global positioning system (GPS) functions to estimate the number of locations or the amount of distance traveled by participants[216,217]. The ability to collect passive data, for long periods of time and with no effort on the part of the subjects, opens up a new world of information derived from big data[218]. It is possible that cognitively relevant indices can be obtained from passive data, but this remains to be demonstrated.

Brain network organization

As mentioned above, studies of isolated brain regions have shifted to a focus on connectivity, which fits with one of the most influential theories of the pathophysiology of schizophrenia, that of neural disconnection[219,220]. According to this theory, several features of schizophrenia, including problems in social functioning, arise from an underlying problem in neural connectivity.

Until recently, the field had limited tools to examine connectivity with functional neuroimaging, and most of the work was to examine connections between pairs of regions. One key development has been the change from traditional (i.e., seed-based) connectivity approaches to graph-based methods for examining brain network organization[221]. Graph theory provides powerful quantitative tools for network analyses of brain connectivity and organization. It can characterize network structure by identifying local contributions of individual nodes and connections, as well as the network's global capacity to integrate information[222].

Graph theory studies of schizophrenia have so far produced mixed results[223,224], perhaps because some studies use resting state and others task-based imaging data. Nonetheless, these approaches have tremendous potential for understanding psychiatric conditions. It is likely that schizophrenia, as well as other major mental illness, are associated with specific and characteristic disturbances of network connectivity[225].

CONCLUSIONS

Breakthroughs, incremental steps, and a disappointment

If we look at the developments over the past 5-10 years, it is our impression that most of the advances have been incremental – steps toward a better understanding of the nature and implications of cognition in schizophrenia. Some of these steps were made possible by advances in related areas of science, such as neuroimaging, social neuroscience, big data methods, or neuropharmacology. Also, many of the advances reflected recent empirical maturity, in which meta-analyses were employed to detect signals by combining a large number of studies, or multisite consortia were formed to recruit a large number of subjects with detailed assessments and phenotyping.

Aside from an inevitable march forward with incremental steps, some areas related to cognition in schizophrenia seemed to take large leaps in recent years. An admittedly subjective list of such examples would include the dramatic advances in neuroimaging methods such as connectivity and network analysis methods, the highly informative modelling of the pathway(s) from brain processes to community integration and daily functioning, and the rapid inclusion of methods and concepts from social and affective neurosciences.

In contrast to these areas of impressive impact, we note one area of disappointment. We still do not have powerful methods for cognitive enhancement in schizophrenia. The developments in non-pharmacological methods are impressive, but do not reliably generalize to functionally meaningful improvements. In terms of new medications, substantial enthusiasm in early phase studies has not been born out in larger, and more dispersed, phase III studies. Meaningful cognitive enhancement in schizophrenia appears to be close, but remains elusive.

Implications for subgrouping and the diagnosis of schizophrenia

The US NIMH initiated the Research Domain Criteria (RDoC) project, which provocatively asks whether specific psychiatric diagnoses, such as schizophrenia, will fit with our rapidly growing knowledge from neuroscience[226,227]. As a result of this emphasis, many studies and some multisite consortia are currently recruiting participants across various psychotic disorders, not schizophrenia alone, to address key scientific questions. For example, the Bipolar and Schizophrenia Network for Intermediate Phenotypes Consortium has proposed cognitive-based biotypes that can be compared in terms of their external validity with existing diagnostic classifications[228,229]. Similarly, the Consortium on the Genetics of Endophenotypes in Schizophrenia has closely examined the genetic influences on a wide range of cognitive endophenotypes for schizophrenia, thereby providing a way to identify genetic subgroups of patients or to parse the genetic architecture of the disorder[230,231].

Perhaps a better understanding of brain-based cognitive, emotional and motivational domains will lead to a reorganization of diagnostic groupings. If so, schizophrenia might cease to exist as a separate disorder and could be lumped together with other types of psychosis, or split into biologically validated subtypes. While we can speculate on such long-range possibilities, the fact remains that schizophrenia will not disappear as a diagnosis any time soon. As long as schizophrenia is a diagnosis, a key question will be whether cognitive impairment should be part of the diagnosis. That outcome very nearly happened in the DSM-5, in which cognition was one of several dimensions that was initially slated for inclusion. Very late in the revision process, it was moved from the main body of the manual to Section III, meaning that it requires additional study before being implemented.

The situation is different with the ICD-11 diagnostic guidelines, in which the level of cognitive impairment is listed as a qualifier for schizophrenia[232], meaning that it will be rated after coding the diagnosis, along with other key features of illness, such as positive, negative and depressive symptoms. Cognition was considered to be an appropriate qualifier because it is related to the prognosis and management of the illness. The rationale for inclusion is that knowing something about the level of cognition will help clinicians and families to anticipate the patients' degree of problems and success in work, school, social functioning, or rehabilitation.

This development marks the first time that clinicians throughout the world will be asked to notice, evaluate and record the cognitive status of schizophrenia patients as part of routine diagnosis.

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Cognitive impairment and psychosis in schizophrenia: independent or linked conditions?

Like much else regarding the pathophysiology of schizophrenia, the relationship between cognitive impairment and psychosis is far from elucidated. An undisputed observation is that they frequently co-occur. Green et al[1] provide a scholarly overview of the state of knowledge in this area. However, they do not elaborate on potential reasons underlying the co-occurrence of cognitive impairment and psychosis.

Much of what we observe as clinical neuroscientists is correlational. Severity of scores on the Positive and Negative Syndrome Scale (PANSS) correlate with social and vocational impairment, which in turn correlate with lifetime cumulative antipsychotic drug administration, which correlates with cardiovascular comorbidities. In health and disease, the correlation between two variables is, often, the sum of the genetic and environmental contributions to these effects.

Thus, one possibility is that cognitive impairment and psychosis have a shared etiology – genetic and/or environmental. The "shared etiology" hypothesis can be tested using various methods. Environmental shared etiology is often studied in epidemiological cohort studies. Environmental factors such as obstetric complications, abuse and trauma during childhood, drug abuse, and immigration have all been reported in relation to cognitive impairment, psychosis or both[2]. Genetic shared etiology has been investigated using behavioral genetic methods in twins and siblings, and more recently using molecular genetic methods.

Twin studies can measure the genetic correlation between two traits. A genetic correlation of 1 between trait A and B would imply that all of the additive genetic influences on trait A also impact on trait B. In one such study, the genetic correlation between schizophrenia and IQ was relatively high (r=0.75)[3]. However, as the correlation is only 0.75, close to half of the genetic variance in schizophrenia is actually independent of intelligence, suggesting that both traits have genes with specific effects. When specific cognitive domains rather than IQ were examined, the genetic correlations varied considerably. They were only 0.34 for tests measuring verbal knowledge and 0.79 for tests measuring working memory. In a second study, using a larger sample, the genetic correlation between schizophrenia and IQ was 0.46, suggesting that the majority of the genetic variance in schizophrenia is actually independent of intelligence[3].

With advances in molecular genetics, polygenic risk scores – which reflect the impact of many risk alleles of small effect – can now be used to quantify the role of directly measured risk genes for schizophrenia on specific cognitive domains. Several studies examined the relation between schizophrenia risk genes and IQ in the general population. What these studies examine is whether genetic variants associated with increased risk for schizophrenia would be associated with poorer cognitive performance. Overall, the reported correlations between the schizophrenia polygenic risk score and IQ and working memory were less than 0.1 for childhood, early and late adulthood[4,5]. Similar results were observed for a range of cognitive domains[6]. Looking at the association from the other direction, i.e. whether genetic variants associated with poorer cognitive performance would be associated with increased risk for schizophrenia, the magnitude of associations was small as well (<1% of variance)[6].

Using bivariate genome-wide complex trait analysis to estimate the amount of shared genetic factors between schizophrenia risk and cognitive ability, the genetic correlation between schizophrenia and IQ was 0.2, and that between schizophrenia and working memory was 0.19. In this study, there was no evidence supporting genetic overlap between schizophrenia and measures of verbal knowledge or social cognition[6].

A second possibility is that schizophrenia and cognitive impairment co-occur because both are associated separately with a third factor. For example, studies have shown that schizophrenia is associated with structural brain abnormalities and that IQ is correlated with whole and gray brain matter volumes. It is therefore possible that the genetic correlation between schizophrenia and IQ is explained by the correlation of both traits with brain volume[3].

It is also possible that cognitive impairment is neither an antecedent nor an enduring consequence of schizophrenia, but it represents non-specific brain vulnerability. Since cognitive impairment characterizes almost all mental disorders, as well as neurological disorders, traumatic brain injury, and drug and alcohol abuse[7], and is already present before the onset of most disorders, it seems to be a non-specific indicator of brain vulnerability or brain malfunctioning.

A fourth and less investigated possibility is that schizophrenia and poor cognitive abilities co-occur coincidently. A coincidental hypothesis of psychosis and cognitive impairment would posit the following. Most community-based individuals with borderline-low cognitive abilities, but without any other mental or emotional disturbances, never see a mental health professional and are never labeled with a psychiatric diagnosis. Similarly, persons with encapsulated delusions or hallucinations, which do not lead to disruptive behavior, live in the community and only rarely come to the attention of mental health professionals. It is only the concomitant manifestation of the two, affecting social and vocational functioning, which leads to help seeking and to a diagnosis of schizophrenia. This would be similar to an individual who suffers from congestive heart failure or an individual suffering from degenerative joint diseases. Neither would have serious mobility limitations, although the former would probably avoid effortful walking and the latter would probably use a walking stick. While the two conditions are pathophysiologically unrelated, their concomitant presence would probably lead to severe mobility impair-

ment and probably necessitate the use of a wheelchair.

The probability of two independent events to occur in sequence is the product of the multiply of the probability of each event occurring separately. Hallucinations and delusions are acknowledged by a sizeable minority of the general population (3.2-7.2%)[8]. Approximately one-third of those people report a frequent occurrence of those symptoms. 13.6% of the population have IQ scores 1 standard deviation or more below the mean, a level of cognitive impairment similar to that consistently reported in schizophrenia[9]. Therefore, even if psychotic symptoms and cognitive impairment were independent of each other, it could still be expected that between 0.44% to 0.98% of the general population will experience psychotic symptoms and present with a cognitive impairment, which approximates the lifetime prevalence of schizophrenia of 0.7%[10].

Overall, these results imply that, while the hypothesis of a shared genetic etiology for psychosis and cognitive impairment is not ruled out, the shared genetic liability is likely to be only modest. It is also important to consider that, like with any correlation, genetic correlations do not reveal directionality. Therefore, the path of causation cannot be inferred: lower IQ may increase liability to schizophrenia, or schizophrenia may cause lower intelligence[3].

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The meaning of group differences in cognitive test performance

What does it mean that groups of individuals given a diagnosis of schizophrenia get fewer items correct and respond more slowly than comparison groups on tests of memory, attention, executive functioning, and social cognition? Green et al's answer[1] is unequivocal: the weaker performance is caused by a "cognitive impairment", which is a "primary deficit", arising from a specific neuropathological cause. This "impairment" is viewed as both a vulnerability factor and a "core feature" of schizophrenia. This is a position currently held by a majority of the field and supported by a large evidence base.

However, the question "why do individuals diagnosed with schizophrenia tend to demonstrate weaker neurocognitive performance?" actually remains without a clear answer. The basic data represent group differences on test performance, but this performance is multidetermined. Factors that have been found to influence the cognitive test performance of individuals given a diagnosis of schizophrenia include motivation, effort, dysfunctional attitudes, asociality, stress, negative emotion, and conceptual disorganization[2]. While it is an empirical question the extent to which these factors contribute to poor test performance, it seems fair to assume that accounting for their aggregate impact would significantly reduce the group differences.

The authors – along with the field – claim external validity for the tests: that weaker performance represents a "pervasive and stable" deficit of cognitive processes across situations in everyday life. However, variability in cognitive performance is a common observation[3]. When individuals who perform in the "severely impaired" range on neurocognitive tests are engaged in satisfying and personally meaningful activities – such as playing chess, driving a car, or preparing a complex recipe – they are observed displaying high levels of cognitive function. During these meaningful activities, motivational and cognitive resources become energized and are activated for use. This contrasts with the neurocognitive testing environment, which is rife with factors – such as beliefs about being incapable, inferior, or judged; and completing tasks that are not engaging or meaningful – that de-energize motivation and resources.

Seeing everyday cognition in this more dynamic way across tasks and situations echoes recent work by Cohen et al[4] demonstrating situational variability in alogia and flat affect, which are features that have also traditionally been viewed as stable. It also implies that treatment efforts may be better suited to helping people access their cognitive resources rather than remediate neurocognition. Ultimately, terms like "deficit" and "impairment" are inaccurate as applied to cognition, especially as the literature is dependent on testing conditions that are denuded of the very qualities that allow variability in performance to emerge. Given the multitude of factors responsible for test performance, group differences in performance on these tests cannot simply "reflect" isomorphic representations of "core deficits" in brain pathophysiology.

Turning to the neurological evidence, a similar pattern emerges. Post-mortem studies showed group differences in brain volume between individuals given a diagnosis of schizophrenia and those from the general population. Rather than being evidence of a core cognitive impairment, as had been claimed, the reductions in brain volume turned out to be the result of long-term exposure to antipsychotic medications[5]. Notably, non-human pri-

mates exposed to antipsychotic medications exhibited the same degree of brain volume loss observed in the post-mortem human studies[6]. This is yet another example of group differences not being obvious indices of underlying neuropathology.

Similarly, group differences in functional magnetic resonance imaging and EEG measures have been interpreted as representing a core neurocognitive impairment. Though widespread practice, the assumption that differential neurophysiological activation during neurocognitive tasks indicates neurocognitive impairment is a fallacy that has plagued the neuroscience literature broadly[7]. For example, in Green et al's description of dorsolateral prefrontal cortex (DLPFC) activation, they indicate that some studies find hypoactivation and others hyperactivation of the DLPFC. It is unlikely that both hypoactivation and hyperactivation suggest impairment, yet this is the interpretation that is made. Additionally, group-level neurophysiological differences do not indicate impairment. Musicians show increased neural tissue volume in some regions and decreased volume in others[8]. This does not suggest that musicians have a neurocognitive impairment, but that they have specialized knowledge from repeated practice. Presumably individuals given a diagnosis of schizophrenia have had experiences – such as trauma, exclusion, and positive symptoms – to a greater degree than the general population, which would be expected to manifest in differential neurophysiology.

The developmental course of test performance is often cited as evidence that impaired neurocognition is a core and stable feature of schizophrenia. As Green et al describe, poorer performance is observed prior to onset of the first episode of psychosis and remains relatively stable after a diagnosis is given. However, negative symptoms are also present prior to the onset of the first episode, and both poor neurocognitive performance and negative symptomatology appear to emerge at similar periods of development (approximately age 9) in individuals who later develop schizophrenia[9]. Thus, it is possible that poor neurocognitive performance represents a consequence of negative symptoms such as amotivation, or that other variables (e.g., negative bias and beliefs) may lead to the development of both negative symptoms and poor neurocognitive performance. For example, childhood trauma has been associated with later performance on neurocognitive tests, and laboratory induced social exclusion impairs subsequent neurocognitive performance in healthy individuals[10].

It is also worth emphasizing that neurocognitive performance has failed to predict who will develop a psychotic disorder among individuals at clinical high risk. If neurocognition were a core feature, then it should be associated with the development of the disorder. It would seem more likely that group differences in test performance do not reveal a distinct feature of schizophrenia, but instead an epiphenomenon that arises from amotivation, negative attitudes, trauma history and other aspects of the disorder.

Finally, language matters. It is unfortunate that the authors refer to "schizophrenia patients" throughout the manuscript. Similar to the other absolute terms – "deficit" and "impairment" – this term has inaccurate connotations. Nobody is just a patient, just a diagnosis, or just a collection of deficits. The science of schizophrenia would benefit from focusing on the whole person, with the mental health challenges that make up the diagnosis being just part of the full picture. Knowing the person at his/her best; and being able to accurately and dynamically assess his/her strengths, positive attributes, and beliefs will all be invaluable in this effort. Ultimately, the distance between the person given a diagnosis of schizophrenia and the typical citizen might grow very small indeed.

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Cognition in schizophrenia: a marker of underlying neurodevelopmental problems?

The paper by Green et al[1] provides an extensive and in-depth review of cognition in schizophrenia, supporting the argument that cognitive dysfunction is a core feature of the illness. However, the authors do not fully explore how knowledge about cognition can inform us about the nature and development of schizophrenia. Is cognitive dysfunction a cause, a consequence or a marker of illness?

Both schizophrenia and general cognitive ability are heritable, with a broad polygenic basis. Genome-wide association studies have identified significant associations between intelligence and educational attainment, as a proxy for general cognitive abilities, and genes involved in central nervous system (CNS) development and synapse regulation. Some of these genes overlap with vulnerability genes for schizophrenia. These genetic associations are primarily negative (i.e., higher intelligence – lower schizophrenia risk), but some of them are bidi-

rectional (i.e., higher intelligence – higher schizophrenia risk)[2]. Further analyses indicate a strong protective effect of intelligence on the risk for schizophrenia, and a smaller negative effect of schizophrenia (risk genes) on intelligence[3].

Aspects of cognition are also impaired in relatives of people with schizophrenia, who take an intermediate position between their affected family member and healthy controls[4]. However, the vulnerability to schizophrenia does not appear to be based in an unlucky familial combination of cognitive and environmental risks. An intriguing registry-based study indicates that schizophrenia risk is predicted by the individual's deviation from familial cognitive aptitude (i.e., what is expected from educational attainment and IQ in parents and siblings) and not by cognitive dysfunction *per se*. When cases are matched to controls by educational achievement or IQ, their relatives are found to have better cognitive aptitudes than the corresponding relatives of the controls. These findings point to the existence of a qualitatively different developmental impairment that is associated with schizophrenia risk[5].

A central finding from genome-wide association studies is the link between risk of schizophrenia and the immune system, in particular, the complement system. Studies have identified a new role for complement 4 (C4) in synaptic pruning. Synaptic pruning peaks during adolescence, and is essential for refinement of the CNS and maturation of cognitive abilities. Structurally different variants of C4 genes are associated with differences in C4 expression and with the risk of schizophrenia, supporting the notion that elevated complement activity leading to increased synaptic pruning is a risk factor for schizophrenia. A recent study using patient-derived induced pluripotent stem cells found abnormalities in microglia-like cells and synaptic structures, in addition to increased synaptic pruning in the neuronal cultures. Risk-associated variants of the C4 genes were linked to increased complement uptake in synapses[6]. In line with this, there are indications of poorer memory function linked to increased predicted C4 expression, across patients with schizophrenia and healthy controls[7].

Prospective studies of early cognitive development in children who later developed schizophrenia showed stable deficits in IQ, language, processing speed and executive functioning from infancy. Verbal deficits appear early and are relatively stable, while impairments in processing speed and executive functions increase during adolescence[8]. The widening gap towards healthy adolescence appears mainly to be based in a developmental lag rather than a loss of acquired functions. Studies on groups considered as clinical high-risk (CHR) for psychosis also find significant cognitive dysfunctions. This is particularly the case for those in the CHR group who later experience transition to psychosis. There are, however, no direct indications of a cognitive decline from the prodrome/high-risk state to the onset of the first episode[9].

The main argument for the initial conceptualization of schizophrenia as a neurodegenerative disorder was the presence of cognitive dysfunction and a deteriorating clinical course. However, first episode studies do not find any associations between the duration of untreated psychosis and cognitive dysfunction. Prospective studies of cognitive trajectories from the first episode onwards also show significant cognitive stability, both in short- and long-term. There are some indications of poorer cognitive development in patients with high illness activity during the first year of treatment, but of limited magnitude and balanced by findings of modest cognitive improvements in other subgroups[10].

Taken together, our knowledge about cognition in the early phases of schizophrenia strongly supports the notion of a primarily neurodevelopmental basis for cognitive dysfunction. Cognitive problems may serve as additional stressors increasing psychosis risk, while other symptoms of the disorder may add to cognitive problems. However, current data indicate that cognitive dysfunction is neither a cause nor a consequence of the psychotic process but rather a biomarker of underlying neurodevelopmental problems.

This notion has important clinical implications: while specific treatments may improve one area of dysfunction (cognition or psychotic symptoms) in adults with schizophrenia, this may not translate to other areas. Preventing additional developmental lags in adolescents at high risk might be one of the most effective ways to prevent significant cognitive dysfunction.

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Cognition and disability in schizophrenia: cognition-related skills deficits and decision-making challenges add to morbidity

Schizophrenia contributes 13.4 (95% UI: 9.9-16.7) million years of life lived with disability to the global burden of disease. Its societal costs are immense, with costs derived from productivity loss even larger than direct treatment costs, a pattern observed across different countries and health care systems. Based on these data, disability reduction in schiz-

ophrenia is a priority, yet there are few effective treatments available.

Nonsocial and social cognitive impairment contributes substantially to reductions in everyday functioning and subjective quality of life in persons with schizophrenia. Green et al[1] present and evaluate sophisticated models of the influence of nonsocial and social cognition on functioning, considering moderating variables (e.g., defeatist attitudes, motivation, reward sensitivity) as well as neurobiological correlates and their potential implications. Further, they thoroughly evaluate treatment efforts to date for these deficits, including pharmacological and remediation-based approaches. Among these efforts are exercise interventions, which target physical fitness and have been shown to have beneficial effects on cognitive performance.

Just like with any other chronic disease process, there are multiple factors that contribute to the development of disability in schizophrenia. Obesity and health-related comorbidities are common. Physical fitness is visibly impaired. The presence of these elements shows a correlation with cognitive impairments[2].

One of the issues covered in less detail in Green et al's review is that of functional capacity (the ability to perform everyday functional skills) and its potential mediating effect between nonsocial and social cognition and functional outcomes. In several studies, functional capacity was found to be proximally related to impairments in everyday functioning, with the strongest predictor of deficits in this capacity generally being nonsocial cognition. In addition, when social functional capacity, generally referred to as social competence, is examined for its relationship to functional outcomes, it can be shown that some elements of social cognition predict performance on measures of social competence, which in turn predict informant ratings of everyday social functioning. Thus, impairments in nonsocial and social cognition may be a precursor to functional skills deficits, which then in turn predict impaired everyday outcomes across several domains.

In a related vein, we have recently documented that correlates of poor physical health and fitness are important determinants of disability in schizophrenia that interact with nonsocial and social cognition to complicate functional outcomes. The end result of these physical impairments might prevent people from even leaving their residences and may exacerbate limitations in functional capacity beyond those originating from nonsocial and social cognitive deficits, while generating additional roadblocks to effective deployment of everyday skills that the patients might possess.

We developed a model that integrates these different contributory paths into a unified model of disability in schizophrenia, attempting to isolate the pertinent individual factors (for example, symptoms, cognition, physical functioning) and their interactions, so that they can be approached in a synergistic manner[3].

In analyses of data from the Suffolk County Mental Health Project, we examined the 20-year course of weight gain and its impact on everyday functioning at the 20-year follow-up. We found that weight gain was progressive over the entire period, leading to over 50% of bipolar patients and 60% of schizophrenia patients having a body mass index in the obese range 20 years after diagnosis[4], a striking change from 8% and 20%, respectively, at the time of first diagnosis.

In a separate examination of the everyday functioning of these same patients at the 20-year follow-up, we found that schizophrenia patients, who had a greater prevalence of obesity and worse cognitive performance, also had worse everyday functioning outcomes in terms of sustaining competitive employment and living independently[5]. For both patient samples, cognitive impairment and two indicators of physical functioning, waist circumference and the ability to rapidly and repeatedly rise from a chair (chair stands), were associated with competitive employment. When a logistic regression was used to predict employment, diagnosis accounted for 11% of the variance, with chair stands accounting for 9% and negative symptoms for an additional 5%. The diagnostic effect was likely associated with cognitive differences between the groups, but mobility limitations associated with obesity were excellent predictors of work outcomes. Modeling residential independence, only diagnosis accounted for variance in outcomes.

These findings do not cast any doubt on the importance of cognitive impairments for predictions of everyday outcomes. Rather, they likely suggest that cognitive impairments may contribute to the development of physical limitations. Obesity in schizophrenia is correlated with multiple impairments in nonsocial and social cognition[6]. On the nonsocial side, decision-making regarding dietary choices has been shown to be impaired. Poor dietary quality is common among low socioeconomic status groups, including those with schizophrenia. Fruit and vegetable intake is uncommon compared to the rest of the population. Those dietary choices, combined with the consumption of highly processed energy-dense food, foster obesity[7].

These calorie-dense, highly palatable foods are readily available in industrialized societies, requiring little effort in procurement and preparation. Patients with schizophrenia appear especially vulnerable to this environment, as they consume more food than mentally healthy people, and their food choices are poorer. In addition, very few patients follow a regular physical exercise routine[8] and, amongst those who do, erroneous assumptions about what represents healthy "exercise" prevail. In addition, the same deficits in valuation judgments noted by Green et al in the performance of emotionally neutral problem-solving tasks are present in food choices, with substantial tendencies toward short-term reinforcement rather than delayed gratification and planned food choices.

Further, impairments in functional capacity, known to be driven by cognitive limitations, are also common in relation to food related skills. Several studies have shown that schizophrenia patients are impaired in their ability to plan for and shop for nutritious meals. Their actual performance of cooking skills is also impaired[9]. Using a series of laboratory-based simulation tests, patients with schizophrenia manifested substantially more impairment in their ability to plan

a meal, shop for ingredients, and actually cook the food than healthy controls. These functional deficits were correlated with the severity of negative, but not positive, symptoms, and with executive functioning, but not memory, deficits.

In conclusion, we suggest that cognitive limitations of people with schizophrenia not only correlate with disability directly, but contribute substantially to other skills deficits (functional capacity; social competence) that exacerbate disability outcomes. Poor health and fitness, which add variance to current cognitive assessments for the prediction of disability, can also be traced back to cognitive deficits. The flow-forward cascade of impaired cognition, particularly in domains of reasoning and problem solving and reinforcement valuation, can lead to deficits in functional capacity which then lead to poor dietary and exercise choices, contributing to poor functional outcome.

Thus, influences on outcomes that appear to be unrelated to cognitive deficits may at least partially originate from cognitive limitations and respond to adequate cognitive enhancing treatments.

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Why are there no approved treatments for cognitive impairment in schizophrenia?

The paper by Green et al[1] details the evidence that cognitive impairment associated with schizophrenia (CIAS) remains a tremendous scourge on the lives of millions of people across the world. It is the aspect of the illness that most accounts for the social isolation and functional disability that plagues most people with schizophrenia for their entire lives.

Yet, tragically, there are no pharmacological or behavioral treatments for CIAS approved by any regulatory agencies across the world. Advances in genetics, biology, pharmacology and technology have facilitated the development of targeted treatments across various areas of medicine, especially in oncology, cardiology and immunology. These advances have transformed some illnesses from devastating, life-threatening events to simple annoyances. Why have the tremendous advances in neuroscience, psychopharmacology and genetics not provided patients with CIAS similar relief?

The most obvious consideration is the amount of investment that is being made in the development of treatments. The 2018 US National Institutes of Health (NIH) budget for research on schizophrenia was $258 million, but for heart disease it was 10 times as much, and for cancer 25 times as much[2]. This disparity is even greater in the pharmaceutical industry, where the overall research and development budget, which in 2017 was $71.5 billion[3], dwarfs government efforts. There are over 1,000 ongoing clinical trials in cancer for every one in CIAS[4] and, contrary to common belief, not because cancer drugs are a safer bet: the latest estimate that a treatment will successfully progress from phase 1 to the US Food and Drug Administration (FDA) approval is 5.1% for cancer indications, very similar to psychiatry at 6.2%[5].

Since many strategies will fail before a success is reached, a large number of attempts is required to find a treatment that is legitimately safe and effective. Further, serendipity flourishes greatest in the most active arenas. Unfortunately, the pharmaceutical industry has not presented nearly as many opportunities for success in CIAS as it has in other illnesses. Perhaps curing cancer is more personally tangible and may appear on the surface to be more morally compelling to investors than improving cognition in the people living in the darkness on the edges of town, and pharmaceutical companies are highly vulnerable to the whims of impressionistic shareholders. It is likely not a coincidence that the drug company listed on clinicaltrials.gov as having the greatest number of ongoing trials for the treatment of CIAS is privately owned.

What may explain why the CIAS trials conducted thus far have not been successful? Are the outcome measures used to assess cognitive and functional change to blame? The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Project developed a cognitive test battery, the MATRICS Consensus Cognitive Battery (MCCB), that was accepted as an FDA gold standard and has been used in most of the later phase trials. Several trials using the MCCB as the primary endpoint have been positive[6], but the one phase 3 program using the MCCB to test the efficacy of an alpha-7 nicotinic agonist was negative and well-publicized. An FDA gold-standard measure is often one of the key components of a registration trial that drug companies are not able to alter, it is thus a natural scapegoat for a failed or negative trial. However, early notions – based on very small samples – that the MCCB had problematic psychometric characteristics were soundly refuted by a

collaborative group pooling data on over 800 patients receiving placebo from 12 separate clinical trials[7].

A more serious consideration for why CIAS trials have been negative is the transition from early to later phase methodologies:

- *Noise*. Larger sample sizes have more statistical power, but larger trials often require methodologies that create noise and weaken power. Single site studies with dedicated investigators are adept at eliminating noise. Later trials with tens or even hundreds of site investigators are often not implemented at each site in the exact same manner.
- *Regulation*. Later phase trials, including pivotal trials, are more likely to adhere to stringent regulatory processes that eliminate some of the bias that is inherent to small studies conducted by individual investigators with conflicts of interests based upon financial and aspirational motives. Greater regulation leads to less bias and fewer positive findings.
- *Regulated endpoints*. A treatment signal is more likely when investigators can match a mechanism of action with an appropriate endpoint (e.g., choosing a processing speed endpoint with a short time frame of follow-up for a stimulant trial), but more difficult to detect with an endpoint determined by regulatory agencies to have general relevance.
- *Simple regression to the mean*. Early phase studies with positive results are forwarded to the next phase. Negative studies are not. Because of the small sample sizes of these trials necessitated by cost concerns, statistical power is low. Therefore, some investigators will lower the threshold for statistical significance of these studies to align their go/no-go decisions with their business priorities, and may include multiple comparisons and *post hoc* analyses without correction. These approaches lead to more type I statistical errors where null hypotheses of no treatment effect are mistakenly rejected. In the next phase of trial, with improved statistical power and the enhanced precision that it brings, no effect of the drug will be found.

Another important consideration for the negative trials to date is that almost all of them have targeted a chronic schizophrenia population with an average age around 40 years old. Has the opportunity to improve cognition passed at that age? Models of brain plasticity suggest that the propagative properties of neurons diminish over time, and it is reasonable that this aging process is accelerated in people with schizophrenia, who are more likely to have comorbid medical conditions, substance use and reduced physical and mental engagement with the environment. Some data have suggested that younger patients may be more responsive to CIAS treatments. The idea of treating CIAS in first episode patients has often been proposed, but completing these trials has been challenging. Several of us have urged for the remediation of cognitive impairment with highly safe treatments prior to the onset of psychosis in vulnerable populations[8,9], but again these trials are challenged by patient recruitment concerns and the length of time required to identify treatment response.

Beyond these questions of study design and implementation are darker considerations. Do we need to wait for a greater understanding of how complex human neural systems operate before we can discover pharmacological and behavioral treatments that interact with them favorably? Or perhaps CIAS is so elemental to the genetic manifestation of a diseased brain that we will never be able to alter it once an infant is born? All of these pessimistic perspectives are possible. However, the history of medicine includes a steady stream of examples where scientists and clinicians whose ideas and compassion were too great to listen to the herd mentality of financial investors and fear mongers. Those with the courage and resources to pursue reasonable hypotheses based upon the limited data we have available now will perhaps be viewed by history as resolute prospectors who invested in the reduction of suffering.

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Innovative methods for improving cognition, motivation and wellbeing in schizophrenia

Neuropsychiatric disorders involve impairment of cognition, motivation and their interaction[1]. Cognitive manifestations include attentional biases, aberrant learning, dysfunctional reward processing, and lack of top-down cognitive control by the prefrontal cortex. These cognitive manifestations are both "cold" or non-emotional and "hot" or social and emotional[2]. From a neurobiological perspective, these relate to two partially segregated loops: the "cold" loop including the dorsal lateral prefron-

tal cortex and the "hot" affective loop including the orbitofrontal cortex and the ventral striatum, with strong connections to the "emotional brain" including the amygdala[2].

There are three major problems in schizophrenia: positive symptoms, cognitive symptoms and motivational deficits, which include negative symptoms. Green et al[3] make a compelling argument that cognitive impairments in both social and non-social domains are core features of the illness. Although antipsychotic medications treat hallucinations and delusions reasonably well, they have little impact on functional outcomes. One of the biggest challenges of this century is how to treat early and effectively the cognitive and motivational deficits in patients with schizophrenia in order to prevent their persistence and ensure the best possible outcome.

Our group has focused on episodic memory impairments in neuropsychiatric disorders. Impaired episodic memory occurs early and strongly relates to functionality in patients with amnestic mild cognitive impairment, Alzheimer's disease and schizophrenia. Episodic memory is also a functional correlate that is impaired in patients with a first episode of psychosis and further declines as the illness becomes more chronic.

This form of new learning and memory has been shown to utilize a neural circuitry including the hippocampus. Changes in hippocampal subfields, including volume loss in the hippocampal stratum layers and the dentate gyrus, have been implicated in memory dysfunction in first-episode and chronic schizophrenia[4].

Although cognitive dysfunction is acknowledged as a target for treatment by the US Food and Drug Administration (FDA), there are no licensed medications currently available. We thus propose that innovative pharmacological and non-pharmacological methods should be developed and implemented further to target *both* cognitive and motivational dysfunction in the symptomatic treatment of schizophrenia and other neuropsychiatric disorders, rather than focussing on diagnostic status.

Interest in the cognitive-enhancing properties of modafinil has been the focus of considerable experimental medicine research over the last two decades. Modafinil is a wakefulness-promoting agent that has been shown to enhance cognitive performance and task-related motivation in healthy volunteers. Modafinil has also been found to have positive effects in clinical populations such as adults with attention-deficit/hyperactivity disorder (ADHD). The precise mechanism for the cognitive-enhancing effects is not clear, but this agent is thought to activate the dopaminergic, glutamatergic, noradrenergic and serotonergic systems in several brain regions, including the prefrontal cortex, hippocampus, hypothalamus and basal ganglia.

It has been shown that modafinil improves episodic memory in patients with schizophrenia[5]. This agent has also been reported to selectively improve spatial working memory and emotional processing (e.g. affect recognition, which might help social and occupational functioning) in first-episode schizophrenia, as well as a range of cognitive domains – including attentional set shifting, visual memory and spatial planning – in chronic schizophrenia[6]. Importantly, there have been no safety concerns about exacerbating psychotic symptoms, and there is no evidence of abuse potential when administering modafinil at 200 mg/day. Simultaneously enhancing cognition and motivation may have broad down-stream effects on patients' functioning, quality of life and wellbeing[6]. It is also possible that improving memory or functioning more generally through cognitive enhancement could help protect against psychotic relapse.

In addition to novel cognitive-enhancing drugs, non-pharmacological interventions also have the potential to target symptoms as low-risk non-invasive options for patients with schizophrenia. Cognitive remediation strategies generate moderate effect sizes on cognition and psychosocial functioning and a smaller effect size on psychiatric symptom severity in schizophrenia[7]. Cognitive training, in particular, has been shown to increase dopamine D_1 receptor density in the brain and produce functional changes in the fronto-parietal network[8].

However, compliance with cognitive training may be problematic, leading to high drop out rates, thus requiring a more motivational approach. To overcome this challenge, a study from our laboratory recently combined cognitive training with gaming technology, showing that playing eight hours of the novel Wizard memory game (www.peak.net) on an iPad improved episodic memory and global functioning in patients with schizophrenia[1]. Importantly, high levels of enjoyment and task-related motivation were maintained throughout all hours of gameplay. Our game was also titrated in difficulty in real-time, akin to personalized medicine, to promote a sense of achievement whilst maintaining high levels of motivation and improving performance over time. We therefore maximized the effects of cognitive training by directly increasing active engagement with the intervention.

Advantages of incorporating a cognitive training programme into a game are that it helps de-stigmatize treatment, since everyone plays games; it is convenient, as travel to a hospital or clinic is not necessary and specialist equipment is not required; it is not associated with side effects; and it is highly rewarding. Use of exciting new technology in mental health, in particular gaming platforms, could reach more patients inexpensively, including adolescents at ultra-high risk of schizophrenia. Gamified cognitive training could also yield benefits for mood and self-esteem, as improvements in memory function following gameplay could be attributed to the self rather than a drug.

In order to identify changes in cognition, emotion and motivation, there is a need for objective and reliable measures for evaluating affective domains. EMOTICOM (www.cambridgecognition.com) is a novel neuropsychological test battery of emotion processing, motivation, impulsivity and social cognition. Recent evidence has shown that this battery is likely to be highly relevant to "hot" cognitive processes in paranoid schizophrenia, as one key aspect implicated in the formation and maintenance of a persecutory delusion is the hostile perception of others, including their beliefs and intentions[9]. EMOTICOM could also be used

in treatment development and efficacy research, such as the evaluation of the neuropeptide oxytocin, which has shown some effects on social cognition in schizophrenia.

Interventions such as oxytocin or modafinil, used in combination with gamified cognitive training, may synergize to increase plasticity and learning, promoting improvement in both "hot" and "cold" cognition as well as in social functioning. Augmentation therapies would be particularly useful for rehabilitating patients who have cognitive impairments that persist even after remission of the more acute symptoms.

If young people with schizophrenia are to have the best chance of realizing their potential and of having good functionality and wellbeing, we will have to move to game-changing initiatives that prioritize early detection and early effective intervention. With a move to first-episode psychosis clinics and research studies focusing on children and adolescents with an ultra-high risk of schizophrenia, interventions that target cognition and motivation can be implemented much earlier in the course of the illness, before "rescuing" cognition is the only option. Good cognition and positive wellbeing are closely linked and both are required for a flourishing society.

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The need to develop personalized interventions to improve cognition in schizophrenia

Green et al[1] provide a review of the evidence on neurocognitive and social cognitive deficits in schizophrenia. These deficits span the course of the disease, starting from the prodrome, and are stable over time. Impairments in neurocognition involve learning and memory, vigilance/attention, speed of processing, reasoning and problem solving, and working memory. Social cognition deficits affect psychological processes implicated in the perception, encoding, storage, retrieval and regulation of information about other people and ourselves. The underlying neurobiological disturbances have their origin in brain networks involving the hippocampus as well as temporal, parietal and prefrontal cortex. Here we discuss the central role of the hippocampus in cognitive processes and the impact of non-pharmacological treatments on this brain structure in schizophrenia patients.

The hippocampus has been implicated in episodic and working memory. In schizophrenia patients, associations were recently detected between hippocampal subregion volumes and cognitive performance in visual and verbal memory as well as working memory domains[2]. Among the most prominently altered hippocampal subregions in schizophrenia are cornu ammonis 4 (CA4)/dentate gyrus (DG) and CA2/3. In post-mortem brains of schizophrenia patients, along with reduced volumes of these subregions, we detected a reduced number of oligodendrocytes (the myelin-forming glia cells) in the left CA4 and a reduced number of neurons in the DG[3]. The reduced number of oligodendrocytes in the left CA4 was related to cognitive deficits in these patients.

These changes might in part be a consequence of disturbed neuro-regenerative mechanisms in the brain[4]. This hypothesis is supported by findings of reduced synaptic proteins and dysregulation of structural synaptic elements in the temporal lobes in schizophrenia. The converging lines of evidence suggest that episodic memory dysfunction in schizophrenia might well be caused by a disturbance of synaptic and neuronal plasticity and disconnectivity[4].

Understanding the underlying neurobiology of cognitive dysfunction is critical to allow researchers to develop pathophysiology-based innovative treatment strategies. So far, however, efforts to develop new pharmacological treatments have been disappointing. Among promising non-pharmacological add-on interventions for cognitive impairments, Green et al[1] propose aerobic exercise. This treatment has been suggested to promote neuroplasticity at the synaptic level and to improve neurogenesis, at least in animal models. Moreover, epigenetic mechanisms may also be involved.

Green et al[1] mention a recent meta-analysis of controlled trials investigating cognitive outcomes of aerobic exercise interventions in schizophrenia. Meta-regression analyses indicated that greater amounts of exercise were associated with greater improvements in global cognition. Among the cognitive domains, aerobic exercise improved working memory, social cognition, and attention/vigilance[5]. Effects on verbal memory were not among the significant results, but this subdomain was only measured in six studies, which limits the strength of findings in this meta-analysis.

To achieve meaningful real-world functional benefits, Green et al suggest to combine cognitive remediation with aerobic exercise. In fact, in a three-month aerobic exercise study, in which bicycle ergometer training augmented with cognitive

remediation was compared with table soccer plus cognitive remediation, we found improvement in everyday functioning of schizophrenia patients measured with the Global Assessment of Functioning (GAF) scale, and in social adjustment measured with the Social Adjustment Scale (SAS-II). The ability to work was associated with improvement in verbal memory and processing speed[6].

Short- and long-term verbal memory scores and cognitive flexibility performance were increased in schizophrenia patients and healthy controls receiving the endurance training augmented with cognitive remediation at three months versus six weeks, but this was not observed in those receiving table soccer augmented with cognitive remediation[6]. This finding supports the need to perform long-lasting training programs to improve cognitive deficits in this severely affected patient group. We previously detected an increase in hippocampal volume after a three-month endurance training, but we could not replicate this finding in our second study.

On the basis of the hypothesis that the individual genetic risk load for schizophrenia – which contributes to neuroplastic processes in the brain – plays a role in the response to aerobic exercise, we calculated the schizophrenia polygenic risk score in our sample. Volume changes in the left CA4/DG at three months versus baseline were significantly influenced by polygenic risk score in schizophrenia patients performing aerobic exercise. A larger genetic risk burden was associated with a less pronounced volume increase or even a volume decrease over the course of the exercise intervention[7].

Results of exploratory enrichment analyses reinforced the notion that genetic risk factors modulate biological processes that are tightly related to synaptic ion channel activity, calcium signaling, glutamate signaling, and regulation of cell morphogenesis[7]. Interestingly, the CA4/DG region was again most affected, which corresponds to our post-mortem findings in schizophrenia[3]. We hypothesize that a high polygenic risk may negatively influence neuroplastic processes during aerobic exercise in schizophrenia, indicating a gene x environment interaction.

Besides the need to replicate these findings in independent samples, future studies are needed to identify those patients who benefit from aerobic exercise interventions and to assess the effects of individual genetic and environmental factors on treatment-induced improvements in cognitive abilities. This would contribute to the development of a personalized approach to improve cognition in schizophrenia.

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Cognitive impairment as a diagnostic criterion and treatment target in schizophrenia

Green et al[1] mention the ongoing debate on whether cognitive impairment should be part of the diagnostic criteria for schizophrenia. In the preparatory work for the DSM-5, this impairment was initially proposed for inclusion, yet the final decision was that it requires additional study before being included. I would like to elaborate on this point and on the implications of the inclusion of cognitive impairment as a diagnostic criterion for the treatment of schizophrenia.

Despite the fact that cognitive impairment is as prevalent as delusions, hallucinations or thought disorder, is present even before the development of psychosis, and is persistent rather than intermittent, a number of reasons might have contributed to the decision not to include it in the criterion A for the diagnosis of schizophrenia.

The first reason is that, contrary to the symptoms/signs included in that criterion, which can be elicited and/or observed during a diagnostic interview, cognitive assessment requires the administration of a battery of psychometric tests. This is time consuming and requires specific training and skills that are common in research settings but difficult to apply in daily clinical practice. Moreover, since cognitive impairment in schizophrenia is pervasive rather than test-specific, it is difficult to establish what pattern of dysfunction and what degree of severity should be present to fulfill the criterion. Finally, a cognitive impairment of the magnitude typically manifested in schizophrenia is too common in other mental disorders as well as in the general population to constitute a useful diagnostic criterion *per se*.

Despite these reservations, it is possible that in the next edition of the ICD, and perhaps also the DSM, cognitive impairment will become a criterion rather than an associated feature in the schizophrenia diagnostic category. Indeed, as Green et al point out, knowing something about the level of cognition in a patient would help clinicians and families to anticipate the degree of problems and success in work, school, social functioning, or rehabilitation.

Since cognitive impairment is present in several mental disorders[2], it will certainly appear as a central dimension in systems such as the Research Domain Criteria (RDoC). It is possible that cognitive

dysfunction represents the distal manifestation of a variety of brain disorders, from head trauma to brain degenerative diseases to schizophrenia. It may then be similar to pain, nausea and dyspnea, which represent the distal manifestation of many somatic disorders. This brings forward the question of cognitive impairment as a treatment target.

Over the last four decades, many investigators and pharmaceutical companies have conducted trials in patients with a diagnosis of schizophrenia using constructs of cognitive functioning as the main outcome[3]. Initially, it was believed that second-generation antipsychotics would be able to ameliorate cognitive impairment but, when it became clear that this was not the case, almost every known neurotransmitter was targeted. Basic science and some clinical data pointed out that dopaminergic, nicotinic and NMDA receptors[4-7] might all be a target for pro-cognitive drugs.

The basic design of the trials testing pro-cognitive compounds involved the recruitment of symptomatically stable schizophrenia patients and the administration of the pro-cognitive experimental drug or placebo added to an antipsychotic drug for several weeks to a few months. The add-on design was employed because of the belief that psychosis is the primary abnormality in schizophrenia and/or because of concerns that, in the absence of maintenance treatment with antipsychotics, patients would be destabilized, which in turn would worsen their cognitive performance. A few projects produced positive results in the proof of concept phases but negative results in confirmatory trials.

A range of methodological limitations has been discussed in an attempt to explain the failure of such trials. Selection of specific outcome measures, length of trial, comorbidities, poor patient's cooperation with testing procedures, large placebo effects, overlap with negative symptoms, were only some of these limitations. It could also be hypothesized that, in the add-on design, dopamine blocking antipsychotics impair performance on cognitive tests[8], so that no cognitive improvement can be elicited.

Furthermore, if in many individuals cognitive performance is, in fact, independent of psychosis, this may have important ramifications for study design. The most important implication is that the trials should preferably not include dopamine blocking drugs. Moreover, if indeed psychosis is only coincidentally superimposed on cognitive impairment, then the pharmacological intervention should be effective in patients without schizophrenia and in non-mentally ill individuals with low cognitive performance. Hence, new pharmacological agents should be first tried in these individuals, to avoid the confounding effects of other schizophrenic symptoms and of antipsychotic drugs.

In sum, until a better understanding emerges, although the future editions of the main diagnostic systems will likely include cognitive impairment as a criterion for the diagnosis of schizophrenia, the possibility that the schizophrenia syndrome represents the coincidental manifestation of several distinct mental abnormalities should not be ignored, with the relevant implications for diagnostic systems as well as for pharmacological and non-pharmacological treatments.

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Examining the independent and joint effects of molecular genetic liability and environmental exposures in schizophrenia: results from the EUGEI study

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Schizophrenia is a heritable complex phenotype associated with a background risk involving multiple common genetic variants of small effect and a multitude of environmental exposures. Early twin and family studies using proxy-genetic liability measures suggest gene-environment interaction in the etiology of schizophrenia spectrum disorders, but the molecular evidence is scarce. Here, by analyzing the main and joint associations of polygenic risk score for schizophrenia (PRS-SCZ) and environmental exposures in 1,699 patients with a diagnosis of schizophrenia spectrum disorders and 1,542 unrelated controls with no lifetime history of a diagnosis of those disorders, we provide further evidence for gene-environment interaction in schizophrenia. Evidence was found for additive interaction of molecular genetic risk state for schizophrenia (binary mode of PRS-SCZ above 75% of the control distribution) with the presence of lifetime regular cannabis use and exposure to early-life adversities (sexual abuse, emotional abuse, emotional neglect, and bullying), but not with the presence of hearing impairment, season of birth (winter birth), and exposure to physical abuse or physical neglect in childhood. The sensitivity analyses replacing the a priori PRS-SCZ at 75% with alternative cut-points (50% and 25%) confirmed the additive interaction. Our results suggest that the etiopathogenesis of schizophrenia involves genetic underpinnings that act by making individuals more sensitive to the effects of some environmental exposures.

Key words: Schizophrenia, psychosis, genetics, environment, gene-environment interaction, polygenic risk, childhood trauma, cannabis, bullying

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Schizophrenia is a complex phenotype characterized by reality distortion, cognitive alteration and negative symptoms. Although the prevalence of schizophrenia spectrum disorders is relatively low – approximately 0.47% for schizophrenia (the poor outcome fraction) and 3.0% for other clinical diagnoses of psychotic disorders[1] – they account for a tremendous personal, economic and societal burden, with 218 disability adjusted life years (DALYs) per 100,000[2], making schizophrenia the fifth leading cause of DALYs in the age group of 15-44 years. These figures indicate that there is an urgent need for breakthroughs in prevention, diagnosis and management of schizophrenia and related disorders, which can be achieved by increased understanding of etiopathology.

Decades of work consistently yielding high heritability estimates document the role of genetic background in the etiopathology of these disorders[3,4]. In agreement with findings from early family-based studies, recent results from the Danish nationwide registers confirm that the heritability estimates range from 73% for schizophrenia spectrum disorders to 79% for narrow schizophrenia diagnosis[5].

Based on these findings from the field of quantitative genetic epidemiology, molecular genetics has emerged as arguably

the most popular area of investigation in research targeting schizophrenia spectrum disorders. Easy and low-cost access to high-throughput techniques has increased genetic resolution. The Psychiatric Genomics Consortium[6] was founded to achieve the power required to detect small effect sizes in a genome-wide association (GWA) analysis. The Schizophrenia Working Group of the Consortium identified 108 genome-wide significant loci[7], and the number of novel genetic variants keeps growing as a function of sample size[8]. GWA findings, in line with the half-century-old polygenic theory of schizophrenia[9], established that a large fraction of the genetic risk is explained by many common genetic variants with very small effects sizes.

However, the proportion of the genetic liability accounted for by single nucleotide polymorphisms (SNPs) detected in current GWA arrays represents only a fraction of the effect that was suggested by heritability estimates from twin studies. In other terms, there is a large "heritability gap" between twin and molecular genetics studies[10]. The most likely explanation for this gap is that part of the genetic effect documented by twin studies is contingent on environmental factors shared by individuals growing up in the same family[10]. The etiology of psychosis spectrum disorder is likely to involve genetic underpinnings that act by making individuals more sensitive to the effects of environmental exposures or by driving individuals to higher exposure rates[11].

In parallel to the growing knowledge base in genetics, environmental research into schizophrenia has produced consistent findings over years. Observational studies have identified various exposures associated with risk of psychosis spectrum disorder at different levels of evidence, with varying magnitude of the effect size estimates. These environmental risk factors include cannabis use, childhood adversities (e.g., sexual abuse, emotional neglect), peer-bullying, urban environment, proxies of social exclusion (e.g., ethnic minority, immigration, and hearing impairment), season of birth, and obstetric and pregnancy complications[12,13].

Although findings from empirical investigations relying on surrogates of genetic risk (i.e., familial history of schizophrenia) argue for a strong influence of environment in moderating genetic vulnerability[11], operationalizing and translating these findings by using molecular candidate-gene approaches have been challenging tasks[14].

The utilization of polygenic risk score (PRS) as a single metric of molecular genetic risk has considerably increased the power to detect associations with phenotypes as well as gene-environment interactions. Currently, the PRS for schizophrenia (PRS-SCZ) of a subject can be estimated by summing the log odds ratios of individual SNPs multiplied by the number of risk alleles present at the corresponding loci[15]. PRS-SCZ has been shown to explain up to 7% of variation on the liability scale to schizophrenia, at least when using the latest release of the Psychiatric Genomics Consortium in patients with more chronic forms[7].

We recently discussed the challenges of evaluating the role of environmental exposures in psychiatry and the need to use exposure-wide systematic approaches to separate genuine strong signals from selective reporting[16]. Guided by this, we aimed to analyze the main and joint associations of environmental exposures and PRS-SCZ in a cross-sectional sample that was specifically collected to test for gene-environment interactions in schizophrenia.

METHODS

Study population

This case-control gene-environment interaction study used data from the Work-package 6 (WP6) of the European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EUGEI)[17] and the Genetic Risk and Outcome of Psychosis (GROUP) study within the EUGEI[18]. Data were collected between 2010 and 2015 in the Netherlands, Turkey, Spain and Serbia.

Patients were diagnosed with schizophrenia spectrum disorders according to the DSM-IV-TR (average duration of illness since age of first contact with mental health services = 9.9 years). The diagnosis was later confirmed by the Operational Criteria Checklist for Psychotic and Affective Illness[19] in the EUGEI WP6, and the Schedules for Clinical Assessment in Neuropsychiatry[20] or the Comprehensive Assessment of Symptoms and History[21] in the GROUP. Unrelated controls with no lifetime psychotic disorder were recruited from the same population as the cases. Exclusion criteria for all participants were a diagnosis of psychotic disorder due to another medical condition, a history of head injury with loss of consciousness, and an intelligence quotient <70.

A total of 1,866 patients and 1,583 healthy participants with genotype data available were included. As the predictive power of PRS-SCZ has not been established in people of non-white ethnic origin[22], the present analyses were restricted to participants of Caucasian white ethnic origin. The final sample included 1,699 patients and 1,542 unrelated controls.

The projects were approved by the medical ethics committees of all participating sites and conducted in accordance with the Declaration of Helsinki. All respondents provided written informed consent. Participants below the age of 18 signed an assent; parent(s) also signed an informed consent.

To achieve high quality and homogeneity in clinical, experimental and environmental assessments, standardized instruments were administered by psychiatrists, psychologists or trained research assistants who completed mandatory on-site training sessions and online training modules, including interactive interview videos and self-assessment tools[17,18]. Both on-site and online training sessions were repeated annually to maintain high inter-rater reliability throughout the study enrollment period.

Environmental exposures

Within the limits of data availability, we sought to examine all the environmental exposures that have previously been associated with schizophrenia spectrum disorders.

Childhood adversity was assessed using the Childhood Trauma Questionnaire Short Form (CTQ)[23]. This consists of 28 items, rated on a 5-point Likert scale, measuring five domains of maltreatment (emotional and physical neglect; emotional, physical and sexual abuse). The psychometric characteristics of the translated versions (Spanish, Turkish, Dutch and Serbian) of the CTQ have been comprehensively studied[24-26]. To dichotomize each childhood adversity domain (0="absent" and 1="present"), consistent with previous work in the EUGEI[27], we used the following cut-off scores for each domain: ≥9 for emotional abuse; ≥8 for physical abuse; ≥6 for sexual abuse; ≥10 for emotional neglect; and ≥8 for physical neglect.

Cannabis use was assessed by a modified version of the Cannabis Experiences Questionnaire[28] in the EUGEI WP6 (0="none"; 1="only once or twice"; 2="a few times a year"; 3="a few times a month"; 4="once or more a week"; 5="everyday"), and by the L section of the Composite International Diagnostic Interview (CIDI)[29] in the GROUP (0="none"; 1="less than weekly"; 2="weekly"; 3="daily"). Consistent with previous work[30-32], a binary regular cannabis use variable was constructed by using the cut-off value of once or more per week during the lifetime period of most frequent use.

In accordance with previous studies investigating the association between season of birth and schizophrenia in the Northern hemisphere sites[33], the high-risk birth period was defined based on the winter solstice (December-March), and a binary winter-birth exposure was constructed.

Hearing impairment was defined based on self-reported hearing impairment in the last 12 months (0="absent" and 1="present").

The history of bullying by peers (emotional, psychological or physical violence) before 17 years of age was assessed using the short version of the Retrospective Bullying Questionnaire (RBQ)[34,35], that measures the severity of the bullying experience: 0="none"; 1="some (no physical injuries)"; 2="moderate (minor injuries or transient emotional reactions)"; 3="marked (severe and frequent physical or psychological harm)". Exposure to childhood bullying was dichotomized using ≥1 as the cut-off point (0="absent" and ≥1="present").

Genetic data processing

Samples of all individuals were genotyped at Cardiff University Institute of Psychological Medicine and Clinical Neurology, using custom Illumina HumanCoreExome-24 BeadChip genotyping arrays containing probes for 570038 genetic variants (Illumina, San Diego, CA). Genotype data were called using the GenomeStudio package and transferred into PLINK format for further analysis.

Quality control was conducted in PLINK v1.07[36] or with custom Perl scripts. Variants with call rate <98% were excluded from the dataset. Hardy-Weinberg equilibrium p-value was calculated separately in Turkish, Northern European and Southern European samples. Variants with Hardy-Weinberg equilibrium p-value <1e-6 in any of these three regions were excluded from the dataset. After quality control, 559505 variants remained.

Samples with call rate <98% were excluded from the dataset. A linkage disequilibrium (LD) pruned set of variants was calculated using the --indep-pairwise command in PLINK (maximum r^2=0.25, window size=500 SNPs, window step size=50 SNPs) and used for further analyses. Homozygosity F values were calculated using the --het command in PLINK, and outlier samples (F<–0.11 or F>0.15) were excluded. The genotypic sex of samples was calculated from X chromosome data using the --check-sex command in PLINK, and samples with different genotypic sex to their database sex were excluded.

Identity-by-descent values were calculated for the sample in PLINK. Samples with one or more siblings among the genotyped samples according to the database but no identified genotypic siblings (defined as PI-HAT >0.35 and <0.65) were excluded. After these were removed from consideration, samples with two or more siblings in the database that were not supported by the genotypic data were also excluded.

After visually observing clustering of errors by genotyping chip, we decided to exclude chips with a high proportion of errors. All samples on chips with five or more sample exclusions due to heterozygosity or call rate (out of 12 possible samples) were excluded. All samples on chips with four or more sample exclusions due to sex or relative checks were also excluded, unless their identity was corroborated by concordance between database and genotype relatedness data with a sample on another chip.

Principal components were calculated in PLINK using LD pruned variants after combining the dataset with the Thousand Genomes reference. Due to the inherently multi-population nature of the dataset and the variety of possible analyses, no exclusions were made to the whole dataset based on this analysis. Population effects were corrected for separately in individual analyses.

After quality control, genotypes were imputed on the Michigan Imputation Server using the Haplotype Reference Consortium reference panel (version 1.1) and the programs Eagle for haplotype phasing and Minimac3 for imputation[37,38]. After imputation, variants with an imputation r^2>0.6, minor allele frequency (MAF) >0.1% and call rate >99% were retained (8277535 variants). Best-guess genotypes were generated from genotype probabilities using PLINK.

PRS-SCZ was constructed using summary statistics from the Psychiatric Genomics Consortium genome-wide association study, excluding samples present in the GROUP data[7]. Clumping was performed in imputed best-guess genotypes for each dataset using PLINK (maximum r^2=0.2, window size=500kb, minimum MAF=10%, minimum imputation information (INFO) score=0.7), and variants within regions of long-range LD around the genome (including the human ma-

jor histocompatibility complex) were excluded[39]. PRS-SCZ was then constructed from best-guess genotypes using PLINK at ten different p-value thresholds (1, 0.5, 0.3, 0.2, 0.1, 0.05, 0.01, 1×10^{-4}, 1×10^{-6}, 5×10^{-8}). Consistent with previous research in the field[40-43], we used p=0.05 for our primary analysis, as this threshold explained most variation in the phenotype in the Psychiatric Genomics Consortium analysis[7].

To be able to compare our estimates from the current sample with the previously reported estimates of the proportion of variance explained by PRS-SCZ, a logistic regression model was applied to test the association of PRS-SCZ with case-control status (adjusted for ancestry using the first ten principal components), and Nagelkerke's R^2 was calculated. PRS-SCZ discriminated cases from controls (odds ratio, OR=1.30; 95% CI: 1.25-1.34; p<0.001; Nagelkerke's R^2=0.15), after also controlling for age, sex and country (OR=1.30; 95% CI: 1.26-1.35; p<0.001; Nagelkerke's R^2=0.20).

PRS-SCZ was dichotomized using the quartile cut-off points based on the control distribution of PRS-SCZ within each country (to account for differences in PRS-SCZ between countries that may arise due to ethnic variation). The highest quartile (PRS-SCZ > 75% of the controls) was considered the binary genetic risk state for schizophrenia (hereafter: PRS-SCZ_{75}).

Statistical analyses

All analyses were carried out using the STATA version 15.0[44]. Random intercept multilevel logistic regression models, taking into account clustering of participants within countries, were applied to test the univariate associations of exposures and PRS-SCZ_{75} with case status. For each exposure, gene-environment correlation was tested using multilevel logistic regression models in the control sample. To test gene-environment interaction, additive models were chosen over multiplicative models prior to data collection (EUGEI consortium meeting, December 14, 2013), because they provide superior representation of biological synergy[45] and inform public health decisions within the sufficient cause framework[46,47].

To test the joint effects of environmental exposures and genetic score, we entered the four states occasioned by the combination of each exposure and binary PRS-SCZ risk state (PRS-SCZ_{75}) as independent variables (three dummy variables with no-risk state as the reference category), and case status as the dependent variable, in multilevel logistic regression models.

We tested for departure from additivity using the interaction contrast ratio, also called the relative excess risk due to interaction (RERI). The RERI is considered the standard measure for interaction on the additive scale in case-control studies[48]. The RERI was estimated as ($OR_{exposure\&PRS\text{-}SCZ75} - OR_{exposure} - OR_{PRS\text{-}SCZ75} + 1$)[49]. A RERI greater than zero was defined as a positive deviation from additivity, and considered significant when the 95% CI did not contain zero. Using the ORs derived from each model, the RERIs for each model were calculated using the delta method.

As a sensitivity measure, the alternative bootstrap percentile method[50] (N=1,000 bootstrap replications) was applied to estimate the bootstrapped 95% CI for the RERI. All models were controlled for *a priori* covariates (age and sex), while models including PRS-SCZ_{75} were additionally adjusted for ancestry, using the first ten principal components accommodating to the general recommendations. Following the extension to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) reporting guidelines[48], the interaction analyses were reported using a single reference category including the separate and joint effects of PRS-SCZ_{75} and each exposure in strata of exposure and PRS-SCZ_{75}.

The analyses were also conducted on imputed data, given missing observations in environmental exposure assessments. Under the assumption of missing at random, the multiple imputation chained equation model[51] with 20 imputations restricted to in-range values was applied (relative efficiency ranging between 97% to 99%). Imputed data were similar to observed values in the original dataset. All analyses were run on multiply imputed data, and estimates were pooled using Rubin's rules[52].

To test the robustness of our findings, sensitivity analyses of binary genetic risk thresholds were conducted using the PRS-SCZ cut points at 50% and 25% of the controls. The nominal significance threshold was set at p=0.05.

RESULTS

Data concerning age, sex and environmental exposures in cases and controls are reported in Table 1.

All exposures except winter birth were associated with case status, also after adjusting for age and sex. Table 2 presents the unadjusted and adjusted ORs for PRS-SCZ_{75} and each of the exposures associated with case status.

Except for physical abuse, there was no evidence for gene-environment correlation, as PRS-SCZ_{75} was not associated strongly or significantly with exposures in the control group (Table 3). Physical abuse was associated with PRS-SCZ_{75} (adjusted OR=1.84; 95% CI: 1.19-2.84; p=0.006).

Table 4 reports the interactive effects of PRS-SCZ_{75} and the exposures on the case status. There was evidence for additive interaction between PRS-SCZ_{75} and regular cannabis use (RERI=5.60; 95% CI: 0.88-10.33; p=0.020), childhood bullying (RERI=2.76; 95% CI: 0.29-5.23; p=0.028), emotional abuse (RERI=5.52; 95% CI: 2.29-8.75; p<0.001), sexual abuse (RERI=7.61; 95% CI: 2.05-13.17; p=0.007), and emotional neglect (RERI=2.46; 95% CI: 0.98-3.94; p=0.001), respectively. Figure 1 visualizes the significant interaction effects on an additive scale. No evidence was found for significant additive interaction effects between PRS-SCZ_{75} and physical abuse, physical neglect, hearing impairment, and winter birth.

Analyses using the alternative bootstrap percentile method for estimating additive interactions yielded similar results (data not shown). The sensitivity analyses replacing the *a priori* set PRS-SCZ_{75} as the genetic risk in the models with the alternative cut-points of PRS-SCZ (50% and 25%) confirmed that additive interaction was evident for regular cannabis use,

Table 1 Demographic variables and environmental exposures in cases and controls

	Total	Controls	Cases	Missing rates
Age (years, mean±SD)	32.4±9.8	33.4±10.6	31.5±9.0	
Sex				
Male	1,951 (60.2%)	762 (49.4%)	1,189 (70.0%)	
Female	1,290 (39.8%)	780 (50.6%)	510 (30.0%)	
Cannabis use				
No	2,390 (78.6%)	1,366 (91.2%)	1,024 (66.5%)	202 (6.2%)
Yes	649 (21.4%)	132 (8.8%)	517 (33.5%)	
Bullying				
No	1,947 (72.3%)	1,101 (83.7%)	846 (61.4%)	547 (16.9%)
Yes	747 (27.7%)	215 (16.3%)	532 (38.6%)	
Emotional abuse				
No	2,019 (73.0%)	1,230 (84.8%)	789 (60.0%)	475 (14.7%)
Yes	747 (27.0%)	221 (15.2%)	526 (40.0%)	
Physical abuse				
No	2,477 (88.7%)	1,362 (93.0%)	1,115 (84.0%)	450 (13.9%)
Yes	314 (11.3%)	102 (7.0%)	212 (16.0%)	
Sexual abuse				
No	2,269 (81.5%)	1,309 (90.1%)	960 (72.1%)	456 (14.1%)
Yes	516 (18.5%)	144 (9.9%)	372 (27.9%)	
Emotional neglect				
No	1,254 (45.3%)	789 (54.3%)	465 (35.4%)	473 (14.6%)
Yes	1,514 (54.7%)	664 (45.7%)	850 (64.6%)	
Physical neglect				
No	1,804 (64.8%)	1039 (71.3%)	765 (57.7%)	457 (14.1%)
Yes	980 (35.2%)	419 (28.7%)	561 (42.3%)	
Winter birth				
No	1,989 (63.2%)	951 (63.0%)	1,038 (63.4%)	94 (2.9%)
Yes	1,158 (36.8%)	559 (37.0%)	599 (36.6%)	
Hearing impairment				
No	2,869 (92.5%)	1,437 (95.6%)	1,432 (89.7%)	141 (4.4%)
Yes	231 (7.5%)	66 (4.4%)	165 (10.3%)	

childhood bullying, emotional abuse, sexual abuse, and emotional neglect across all PRS-SCZ cut-points (data not shown). The results from the analyses performed in the imputed data were similar (Table 5).

DISCUSSION

In this study examining the main and joint associations of environmental exposures and genetic liability with schizophrenia spectrum disorder, evidence emerged for a positive additive interaction of genetic liability with regular cannabis use and childhood adversity domains (sexual abuse, emotional abuse, emotional neglect, and childhood bullying).

To the best of our knowledge, our study is the first to report that the sensitivity to adverse life events during childhood and exposure to cannabis is moderated by genetic risk state for schizophrenia (PRS-SCZ_{75}). Put simply, the positive additive interaction between genetic liability and environmental exposure indicates synergy between gene and environment; that is, the combined influence of genetic liability and environmental exposure is larger than the sum of individual effects of each.

In line with previous findings, PRS-SCZ_{75} discriminated cases from controls and all environmental exposures (except for winter birth) were associated with case status. However,

Table 2 Main effects of environmental and genetic risk on case-control status

	Unadjusted main effects		Adjusted main effects[a]	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Cannabis use	4.85 (3.89-6.05)	<0.001	3.96 (3.16-4.97)	<0.001
Bullying	3.01 (2.48-3.65)	<0.001	3.06 (2.50-3.74)	<0.001
Emotional abuse	3.51 (2.93-4.22)	<0.001	3.77 (3.12-4.56)	<0.001
Physical abuse	2.70 (2.10-3.48)	<0.001	2.83 (2.18-3.67)	<0.001
Sexual abuse	3.66 (2.96-4.53)	<0.001	4.11 (3.30-5.13)	<0.001
Emotional neglect	2.52 (2.14-2.96)	<0.001	2.65 (2.24-3.13)	<0.001
Physical neglect	2.32 (1.96-2.75)	<0.001	2.33 (1.96-2.78)	<0.001
Winter birth	1.06 (0.92-1.23)	0.423	1.05 (0.91-1.23)	0.495
Hearing impairment	2.46 (1.82-3.31)	<0.001	2.67 (1.96-3.62)	<0.001
PRS-SCZ_{75}[b]	2.91 (2.48-3.40)	<0.001	2.85 (2.43-3.35)	<0.001

PRS-SCZ_{75} – polygenic risk score for schizophrenia (75% cut-point)
[a]adjusted for sex and age, [b]adjusted for ten principal components

Table 3 Gene-environment correlation between PRS-SCZ_{75} and environmental exposures

	Unadjusted effects		Adjusted effects[a]	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Cannabis use	0.98 (0.61-1.59)	0.949	0.93 (0.57-1.52)	0.771
Bullying	1.27 (0.86-1.86)	0.228	1.28 (0.87-1.89)	0.210
Emotional abuse	1.13 (0.80-1.58)	0.493	1.13 (0.81-1.59)	0.476
Physical abuse	1.82 (1.18-2.81)	0.007	1.84 (1.19-2.84)	0.006
Sexual abuse	0.79 (0.51-1.22)	0.287	0.79 (0.51-1.23)	0.292
Emotional neglect	1.18 (0.91-1.52)	0.212	1.16 (0.90-1.50)	0.258
Physical neglect	1.18 (0.89-1.56)	0.246	1.19 (0.90-1.58)	0.219
Winter birth	1.13 (0.88-1.45)	0.338	1.13 (0.88-1.45)	0.332
Hearing impairment	1.13 (0.63-2.02)	0.693	1.18 (0.65-2.13)	0.592

PRS-SCZ_{75} – polygenic risk score for schizophrenia (75% cut-point)
[a]adjusted for sex, age and ten principal components

Table 4 Interaction of environmental exposures and PRS-SCZ_{75} on case-control status

	PRS-SCZ_{75}=0		PRS-SCZ_{75}=1		RERI (95% CI)
	N cases/controls	Odds ratio (95% CI)	N cases/controls	Odds ratio (95% CI)	
Cannabis use = 0	556/1042	1.0	468/324	2.84 (2.36-3.40) p<0.001	5.60 (0.88-10.33) p=0.020
Cannabis use = 1	296/102	4.10 (3.13-5.36) p<0.001	221/30	11.54 (7.60-17.51) p<0.001	
Bullying = 0	454/842	1.0	392/259	2.84 (2.31-3.47) p<0.001	2.76 (0.29-5.23) p=0.028
Bullying = 1	296/163	2.97 (2.34-3.76) p<0.001	236/52	7.56 (5.41-10.56) p<0.001	
Emotional abuse = 0	464/939	1.0	325/291	2.39 (1.95-2.94) p<0.001	5.52 (2.29-8.75) p<0.001
Emotional abuse = 1	273/166	3.26 (2.58-4.12) p<0.001	253/55	10.17 (7.33-14.10) p<0.001	
Physical abuse = 0	632/1049	1.0	483/313	2.71 (2.25-3.26) p<0.001	1.64 (–1.07 to 4.34) p=0.235
Physical abuse = 1	107/65	2.97 (2.11-4.17) p<0.001	105/37	6.31 (4.19-9.52) p<0.001	
Sexual abuse = 0	536/993	1.0	424/316	2.68 (2.21-3.25) p<0.001	7.61 (2.05-13.17) p=0.007
Sexual abuse = 1	208/114	3.89 (2.99-5.08) p<0.001	164/30	13.19 (8.60-20.22) p<0.001	
Emotional neglect = 0	273/610	1.0	192/179	2.64 (2.03-3.44) p<0.001	2.46 (0.98-3.94) p=0.001
Emotional neglect = 1	464/495	2.58 (2.10-3.17) p<0.001	386/169	6.69 (5.20-8.59) p<0.001	
Physical neglect = 0	438/804	1.0	327/235	2.81 (2.26-3.50) p<0.001	1.51 (0.00-3.03) p=0.051
Physical neglect =1	308/306	2.42 (1.95 to 3.01) p<0.001	253/113	5.75 (4.36-7.58) p<0.001	
Winter birth = 0	562/733	1.0	476/218	3.11 (2.53-3.82) p<0.001	–0.55 (–1.36 to 0.27) p=0.186
Winter birth = 1	333/414	1.16 (0.96 to 1.41) p=0.123	266/145	2.72 (2.14-3.48) p<0.001	
Hearing impairment = 0	767/1098	1.0	665/339	2.97 (2.51-3.52) p<0.001	1.04 (–2.65 to 4.74) p=0.579
Hearing impairment = 1	107/50	3.11 (2.16 to 4.48) p<0.001	58/16	6.13 (3.43-10.95) p<0.001	

PRS-SCZ_{75} – polygenic risk score for schizophrenia (75% cut-point), RERI – relative excess risk due to interaction
Data adjusted for sex, age and ten principal components

no evidence for an additive interaction with PRS-SCZ_{75} was observed for physical abuse, physical neglect, hearing impairment, or winter birth.

The proportion of variance explained by PRS-SCZ in our sample was comparable to previously reported estimates[53] and the most recent findings from the Psychiatric Genomics Consortium[7]. In this dataset, we strictly conformed to previous definitions of environmental exposures to improve reproducibility and allow comparability. In agreement with previous reports, our univariate analysis demonstrated that the exposures we tested were associated with case status to varying degrees, that were similar to meta-analytical estimates[12,13].

By taking advantage of direct molecular measures of genetic risk, we provided further support for the putative role of gene-environment interaction in schizophrenia spectrum disorder that was observed in previous studies applying indirect genetic liability estimates derived from family-based (e.g., twin, relative) samples[54]. Our findings were corroborated by the results obtained from regression models using different genetic liability thresholds (PRS-SCZ cut-offs at 50% and 25%) and analyses ran in imputed data.

The RERIs and 95% CIs for emotional and sexual abuse were above 2, thereby suggesting a "mechanistic" interaction[49], i.e., that there are individuals who would develop schizophrenia

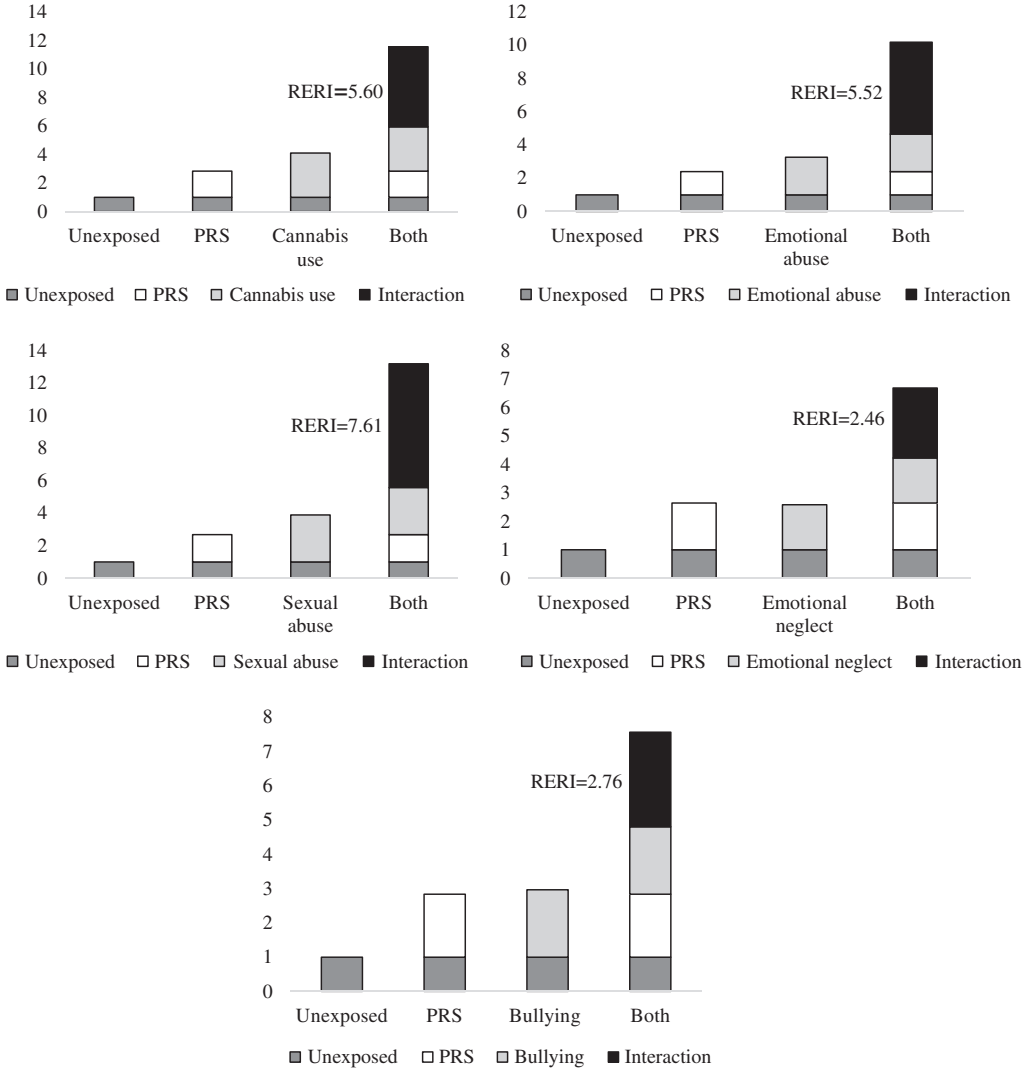

Figure 1 Additive effects of cannabis use, emotional abuse, sexual abuse, emotional neglect and bullying on the association between the polygenic risk score for schizophrenia, 75% cut-point (PRS) and case-control status, adjusted for sex, age and ten principal components; RERI – relative excess risk due to interaction

only when both genetic liability and environmental exposure (emotional or sexual abuse) are present, but would not develop schizophrenia when either genetic liability or environmental exposure is present alone.

PRS-based approaches have recently gained traction in detecting gene-environment interaction. Previously, studies investigated the possible interaction between some genetic polymorphisms possibly linked to the putative biological mechanisms underlying psychosis and cannabis use or childhood adversity. Although SNPs (in various genes) for genetic moderation (e.g., AKT1, COMT, BDNF) were identified, these findings were inconsistent across samples[55] and became secondary once the genome-wide approach took over the scene.

To date, a limited number of studies tested gene-environment interaction across the psychosis spectrum using PRS-SCZ. A pilot study of 80 patients with first-episode psychotic disorders and 110 controls investigating whether PRS-SCZ moderates the association between childhood adversities and psychosis, although yielding main effects of both PRS-SCZ and childhood adversities, was considerably underpowered to detect gene-environment interaction[56]. A recent study demonstrated that intra-uterine environment moderates the association between PRS-SCZ and schizophrenia, and further revealed in the pathway analysis that genes involved in cellular stress response were the main drivers of the gene-environment interaction[57]. In our recent study of a general population twin cohort, we found evidence for positive interaction effects between PRS-SCZ and exposure to childhood adversities to pleiotropically influence momentary emotional regulation and psychosis proneness[58]. Further, a multimodal study combining genetics and imaging techniques reported that the association between PRS-SCZ and cortical maturation in young male adults is moderated by

Table 5 Additive interaction effects of PRS-SCZ$_{75}$ and the environmental exposures on case-control status in the imputed data

	Main effects[a]		Interaction[b]	
	Odds ratio (95% CI)	p	RERI (95% CI)	p
Cannabis use	3.94 (3.15-4.93)	<0.001	5.18 (0.62-9.74)	0.026
Bullying	2.88 (2.36-3.51)	<0.001	2.88 (0.63-5.13)	0.012
Emotional abuse	3.49 (2.88-4.24)	<0.001	5.11 (2.10-8.13)	0.001
Physical abuse	2.65 (2.06-3.40)	<0.001	1.40 (–1.10 to 3.90)	0.272
Sexual abuse	3.74 (3.00-4.66)	<0.001	6.84 (1.77-11.92)	0.008
Emotional neglect	2.51 (2.14-2.95)	<0.001	2.37 (0.90-3.84)	0.002
Physical neglect	2.14 (1.79-2.57)	<0.001	1.42 (–0.05 to 2.88)	0.058
Winter birth	1.06 (0.91-1.23)	0.485	–0.53 (–1.36 to 0.30)	0.209
Hearing impairment	2.68 (1.97-3.66)	<0.001	1.24 (–2.51 to 5.00)	0.516

PRS-SCZ$_{75}$ – polygenic risk score for schizophrenia (75% cut-point), RERI – relative excess risk due to interaction
[a]adjusted for sex and age, [b]adjusted for sex, age and ten principal components

early-life exposure to cannabis[59]. Taken together, while the area of gene-environment research is progressing rapidly toward a more replicable path informed by the use of GWA data, conclusive evidence has yet to emerge.

There are various ways in which our findings can move forward gene-environment interaction research in the GWA era. First, they are useful in providing direction for future pre-registered confirmatory studies. Second, they may open up promising research lines for further exploration of gene-environment interactions in the biological context, such as using biologically-informative pathway scores instead of an aggregate genetic risk score for disease phenotype. These studies may help us investigate both hypotheses for biologically plausible pathways impacted by distinct exposures (e.g., hypoxia-ischemia pathway x obstetric complications and childhood adversities x hypothalamic-pituitary-adrenal axis)[60,61], and putative common final pathways, such as the broad inflammatory pathway which may be influenced by many exposures cumulatively[62].

However, there are important caveats: pathway scores may be less powerful than the overall polygenic scores for phenotypes, and there are almost endless options for selecting and constructing "putative" pathways. Therefore, gene-sets for pathways should be *a priori* defined and frozen at a central repository to avoid data-dredging. Further, study protocols for hypothesis-driven selective exposure and pathway analyses (e.g., regular cannabis use and endocannabinoid pathway) should ideally be either registered or, if this is not possible, agnostic data analyses should be followed through.

In our study, data were collected through extensive interviews by trained psychiatrists, psychologists and research assistants to specifically test the role of gene-environment interaction in schizophrenia. Further, our culturally and geographically diverse sample provided us with the advantage of observing variations in environmental exposures, which increases the power to detect interaction effects[63].

However, some limitations should be acknowledged. First, the cross-sectional design informs only on temporal association and not causality. Nevertheless, cross-sectional analyses arguably remain an essential first step for identifying risk factors and pave the way for future longitudinal studies to investigate gene-environment interaction in evolutionary trajectories. Second, given the sample size and explorative nature of the study, we focused on main and interaction associations of previously established environmental factors and PRS-SCZ. However, the reality is much more complex than current statistical models can accommodate, involving dynamic interactions, causal and non-causal associations within the exposome (e.g., dense correlation matrix of environmental factors influenced by the timing, duration, severity and extent of repeated exposures over time)[16,64]; the genome (e.g., epistasis, redundancy and pleiotropy)[65]; and the phenome (multidimensional syndromal diversity)[66]. Third, instead of the commonly-exercised selective reporting of one exposure at a time, we embraced a quasi-systematic approach to provide an overall picture of the gene-environment interactions findings from this dataset. However, we could not test some other known exposures (e.g., obstetric and pregnancy complications).

In conclusion, by using a molecular genetic risk measure, we have provided further evidence for the role of gene-environment interaction in schizophrenia. Our findings warrant further validation in pre-registered confirmatory research.

APPENDIX

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The symptom-specific efficacy of antidepressant medication vs. cognitive behavioral therapy in the treatment of depression: results from an individual patient data meta-analysis

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A recent individual patient data meta-analysis showed that antidepressant medication is slightly more efficacious than cognitive behavioral therapy (CBT) in reducing overall depression severity in patients with a DSM-defined depressive disorder. We used an update of that dataset, based on seventeen randomized clinical trials, to examine the comparative efficacy of antidepressant medication vs. CBT in more detail by focusing on individual depressive symptoms as assessed with the 17-item Hamilton Rating Scale for Depression. Five symptoms (i.e., "depressed mood", "feelings of guilt", "suicidal thoughts", "psychic anxiety" and "general somatic symptoms") showed larger improvements in the medication compared to the CBT condition (effect sizes ranging from .13 to .16), whereas no differences were found for the twelve other symptoms. In addition, network estimation techniques revealed that all effects, except that on "depressed mood", were direct and could not be explained by any of the other direct or indirect treatment effects. Exploratory analyses showed that information about the symptom-specific efficacy could help in identifying those patients who, based on their pre-treatment symptomatology, are likely to benefit more from antidepressant medication than from CBT (effect size of .30) versus those for whom both treatments are likely to be equally efficacious. Overall, our symptom-oriented approach results in a more thorough evaluation of the efficacy of antidepressant medication over CBT and shows potential in "precision psychiatry".

Key words: Depression, antidepressant medication, cognitive behavioral therapy, depressive symptoms, depressed mood, feelings of guilt, suicidal thoughts, psychic anxiety, general somatic symptoms, precision psychiatry

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Previous studies have consistently shown that both antidepressant medication and cognitive behavioral therapy (CBT) are effective acute phase treatments for depression[1-3]. Conventional meta-analyses indicated that their efficacy is comparable[4], while a recent individual patient data meta-analysis (IPDMA) showed that antidepressant medication is slightly more efficacious than CBT[5].

IPDMA is a relatively new technique in the field of mental health, that has the advantage to use raw data rather than pooling outcomes as in conventional meta-analyses[6]. This results in higher statistical power and provides the opportunity to not only detect relatively small treatment effects but also to assess treatment efficacy in more detail.

Randomized clinical trials (RCTs) on the comparative efficacy of antidepressant medication vs. CBT have primarily focused on changes in overall depression severity, and related outcomes such as response and remission rates. Scales for assessing depression severity are often multifactorial[7-10], and some RCTs have shown that these subscales differ in their response to antidepressant medication vs. CBT[7-9].

Fried et al[10] reported, however, that the multifactorial structure of several commonly used depression scales is not stable over time and, consequently, scale or subscale scores may be inappropriate as outcome measures. It would therefore be valuable to use data of an IPDMA, with its substantial statistical power, to assess the comparative efficacy of antidepressant medication vs. CBT in more detail; namely, by focusing on individual symptoms[11-13].

An additional advantage of a focus on individual symptoms is that it could help in generating hypotheses regarding the differential working mechanisms of treatment. Our group was the first to apply network estimation techniques in research on treatment efficacy, reporting that adjunctive antidepressant medication, relative to psychotherapy alone, was directly related to larger improvements in five specific symptoms (i.e., direct treatment effects), which were subsequently related to larger improvements in two other symptoms (i.e., indirect treatment effects)[13]. Adjunctive medication had no effects, neither directly nor indirectly, on nine other symptoms. As network estimation techniques can identify the complex patterns

in which symptom improvements are related, they have great potential in shedding light on the processes taking place during treatment.

A detailed assessment of the symptom-specific comparative efficacy of antidepressant medication vs. CBT would be important, as it could inform clinicians more precisely about the preferred treatment option for depressed patients in general. This is especially valuable as symptoms differ in their clinical relevance; for example, an effect on "suicidal thoughts" would be more relevant than an effect on "loss of weight".

The findings might also help in identifying patients who, based on their pre-treatment symptomatology, would benefit the most from one treatment relative to the other. That is, patients primarily suffering from symptoms that are affected by one treatment would probably benefit more from that treatment than patients primarily suffering from other symptoms. A focus on individual symptoms may therefore also be an important step in "precision psychiatry".

To our knowledge, this is the first IPDMA that focused on individual symptoms in a more detailed assessment of the comparative efficacy of antidepressant medication vs. CBT in the treatment of depression. In a second step, we used network estimation techniques to test whether the identified effects were direct or indirect. Thirdly, we wanted to explore whether information about the symptom-specific effects of antidepressant medication vs. CBT could help in identifying patients who, based on their pre-treatment symptomatology, are likely to benefit more from one treatment relative to the other.

METHODS

Sample

Our starting point was a recent IPDMA including data of individual patients who participated in RCTs directly comparing antidepressant medication vs. CBT[5]. Only studies including outpatients with a primary diagnosis of a DSM-II, DSM-III or DSM-IV depressive disorder (major depressive disorder or dysthymia), as established by a standardized diagnostic interview, were included. In addition, CBT was required to be manualized and use cognitive restructuring as the main treatment component. Studies focusing on remitted patients or including patients younger than 18 years were excluded. Studies enrolling patients with comorbid general medical disorders were not excluded, and no language restrictions were applied.

Twenty-four studies were identified for the IPDMA. Authors were invited via email to provide original data from their trial. If the authors did not respond to the request after one month, a reminder email was sent and efforts to contact co-authors were made. Authors of four studies were unreachable and authors of another four studies no longer had access to the data. Of the remaining sixteen studies, fourteen[14-27] used the Hamilton Depression Rating Scale (HAM-D) to assess depressive symptoms and were included in the current analyses (responsible for 1,472 patients). Three studies[28-30] were added (responsible for 384 patients) as an update of the dataset.

Of the 1,856 included patients, 843 (45.4%) were randomly assigned to CBT and 1,013 (54.6%) to antidepressant medication (i.e., several studies had double-sized medication conditions). In total, 1,513 (81.5%) had complete pre-treatment data on all individual depressive symptoms, with no difference between antidepressant medication and CBT (82.0% versus 80.9%, p=0.53). Of the patients with complete pre-treatment data, 1,070 (70.7%) had complete post-treatment data on all individual items and comprised the sample for our analyses. Slightly more patients had incomplete post-treatment data in the medication relative to the CBT condition (31.4% versus 26.7%, p=0.04).

Assessment of depressive symptomatology

Individual depressive symptoms were assessed by separate items of the 17-item HAM-D[31], both before and after treatment (i.e., 8-20 weeks after the pre-treatment assessment). The HAM-D includes seventeen items, which are scored from 0 to 4 (items 1-3, 7-11,15-16) or 0 to 2 (items 4-6, 12-14, 17). We chose the HAM-D for the assessment of individual depressive symptoms, as this was the most often used instrument in studies on the comparative efficacy of antidepressants vs. CBT. Overall depression severity was calculated by the sum of all HAM-D items.

Statistical analyses

All non-network analyses were performed using SPSS (version 24). First, baseline characteristics were compared between patients in the medication vs. CBT condition using X^2 statistics for categorical variables (i.e., gender and recruitment setting) and independent samples t-tests for continuous variables (i.e., age, timing of post-treatment assessment, overall depression severity and individual depressive symptom scores). Then, paired t-tests were performed to compare post-treatment to pre-treatment symptom scores for medication and CBT separately. Independent samples t-tests were performed to determine whether change scores of individual symptoms differed between the two treatment conditions.

As a sensitivity analysis, we repeated the above tests in a dataset (N=1,513) in which change scores of patients with missing post-treatment symptom scores were imputed using multiple imputation with baseline symptom scores and sociodemographics as predictor variables.

In a next step, statistical software R (version 3.3.3) was used to estimate a network including treatment condition (medication vs. CBT) and changes in individual depressive symptoms. As this combines a dichotomous variable (treatment condition) with continuous variables (change scores), the network was estimated with package mgm[32] using a mixed graphical model. This package uses the glmnet package[33] to fit penal-

ized generalized linear models to perform neighborhood selection[34]. Package qgraph[35] was used to visualize the network.

In this network, a direct connection between treatment condition and a change in a particular symptom indicates a direct symptom-specific effect, which is independent of the symptom-specific effects on other symptoms. If treatment condition is connected to a particular symptom via one or more changes in other symptoms, it may be interpreted as an indirect symptom-specific effect.

As a sensitivity analysis, we estimated networks including changes in individual symptoms for antidepressant medication and CBT separately. The package network comparison test[36] was used to test whether the networks differed.

Lastly, we explored whether it was possible to identify those patients who are likely to benefit more from one treatment relative to the other. We expected that patients primarily suffering from symptoms that were affected by one treatment would benefit more from that treatment than patients primarily suffering from other symptoms. To test this, two specific severity measures were calculated, based on the simple sum of scores on those pre-treatment symptoms that: a) were significantly impacted by one treatment relative to the other; and b) were the least impacted by one treatment condition relative to the other. We expected that the effect of treatment condition on overall depression severity would be larger in patients with higher scores on the first specific severity measure, but not in patients with higher scores on the second specific severity measure.

RESULTS

Baseline characteristics

Of the 1,070 included patients, 500 received CBT and 570 received antidepressant medication. Patients in the two conditions did not differ in any of the socio-demographic and study characteristics, except for recruitment setting. In addition, no significant differences were found with respect to baseline overall depression severity or any of the individual depressive symptoms (see Table 1).

Symptom-specific comparative efficacy of antidepressant medication vs. CBT

Although overall depression severity improved significantly in both treatment conditions (both $p<0.001$), this improvement was slightly but significantly larger for antidepressant medication than for CBT (Cohen's d=.15) (see Table 2). All individual symptoms also showed significant improvements in both conditions (all p values ≤0.01 for CBT and ≤0.04 for antidepressant medication), but significant differences between the two conditions were found only for the symptoms "depressed mood", "feelings of guilt", "suicidal thoughts", "psychic anxiety" and "general somatic symptoms". These symptoms showed larger improvements for medication than for CBT, although effect sizes were small (Cohen's d ranging from .13 to .16). No significant effects of treatment condition were found for the other twelve symptoms.

The results of the sensitivity analysis based on the imputed dataset were similar; p values differed somewhat, but improvements between conditions remained comparable.

Direct and indirect symptom-specific effects of antidepressant medication vs. CBT

To provide more information about the direct and indirect symptom-specific effects of antidepressant medication vs. CBT, a network was estimated including treatment condition and changes in individual symptoms (Figure 1). The previously identified symptom-specific effects on "feelings of guilt", "suicidal thoughts", "psychic anxiety" and "general somatic symptoms" were, at least partly, direct, indicating that the larger improvements for antidepressants relative to CBT could not be fully explained by any of the other direct or indirect symptom-specific effects.

The previously identified symptom-specific effect on "depressed mood" was fully indirect, suggesting that improvements in the four symptoms that were directly affected by medication relative to CBT resulted, both directly and indirectly, in a larger improvement in "depressed mood".

Sensitivity analyses showed that the two networks including changes in all seventeen individual symptoms did not differ for antidepressant medication vs. CBT ($p=0.77$ for global connectivity, and Holm-Bonferroni corrected p values all ≥0.95 for individual connections).

Identifying patients who benefit more from antidepressant medication relative to CBT

Lastly, we explored whether it was possible to identify patients, based on their pre-treatment symptomatology, who would benefit more from antidepressant medication than from CBT. A specific pre-treatment severity measure was calculated based on the five symptoms that were significantly affected by medication over CBT. As expected, only those patients with the highest scores on this measure improved significantly more from antidepressants than from CBT (Cohen's d=.30, see Figure 2).

As a comparison, another specific severity measure was calculated based on the five symptoms that responded the least to antidepressant medication relative to CBT (i.e., "agitation", "somatic anxiety", "genital symptoms", "loss of weight", and "insight"; all non-significant effects), which was only weakly correlated with the first severity measure (r=.23). As expected, patients with the highest scores on this measure did not show significantly larger improvements for antidepressant medication relative to CBT, but, interestingly, patients with the lowest scores did (Cohen's d=.33, see Figure 3).

Table 1 Sample characteristics

	ADM condition (N=570)	CBT condition (N=500)	p
Gender (% female)	67.0	68.8	0.53
Age at baseline (years, mean±SD)	39.8±12.7	40.0±12.6	0.85
Recruitment setting (%)			<0.001
Community	29.1	18.6	
Clinical	51.2	59.2	
Both	19.6	22.2	
Timing of post-treatment assessment (weeks, mean±SD)	13.2±3.1	13.3±3.1	0.44
Overall depression severity (HAM-D total score, mean±SD)	18.6±4.8	18.3±4.5	0.30
HAM-D scores for individual symptoms (mean±SD)			
Depressed mood	2.2±0.8	2.2±0.8	0.64
Feelings of guilt	1.6±0.9	1.6±0.9	0.25
Suicidal thoughts	0.8±1.0	0.7±0.9	0.14
Early night insomnia	1.0±0.9	1.0±0.9	0.36
Middle night insomnia	1.1±0.8	1.1±0.8	0.57
Early morning insomnia	0.8±0.8	0.7±0.8	0.34
Work and activities	2.4±0.9	2.3±0.9	0.15
Retardation	0.5±0.7	0.6±0.7	0.38
Agitation	0.7±0.9	0.7±1.0	0.22
Psychic anxiety	1.7±0.9	1.7±0.9	0.65
Somatic anxiety	1.6±0.9	1.6±0.9	0.73
Gastrointestinal symptoms	0.6±0.7	0.5±0.7	0.18
General somatic symptoms	1.4±0.6	1.5±0.6	0.38
Genital symptoms	1.2±0.8	1.1±0.8	0.31
Hypochondriasis	0.6±0.8	0.7±0.8	0.16
Loss of weight	0.3±0.6	0.3±0.6	0.26
Insight	0.1±0.4	0.1±0.3	0.33

ADM – antidepressant medication, CBT – cognitive behavioral therapy, HAM-D – Hamilton Depression Rating Scale

DISCUSSION

Principal findings

To our knowledge, this study is the first IPDMA that considered individual depressive symptoms in the comparison of the efficacy of antidepressant medication vs. CBT. Five symptoms (i.e., "depressed mood", "feelings of guilt", "suicidal thoughts", "psychic anxiety" and "general somatic symptoms") showed larger improvements in the medication relative to CBT condition, whereas no differences were found for the twelve other symptoms. Network estimation techniques revealed that all effects were direct, except for the indirect effect on "depressed mood". Our findings further suggest that information about the symptom-specific efficacy could help in identifying those patients, based on their pre-treatment symptomatology, who are likely to benefit more from antidepressant medication than from CBT.

Symptom-specific efficacy of antidepressant medication vs. CBT

Weitz et al[5] recently demonstrated that antidepressant medication was slightly more efficacious in improving overall depression severity than CBT. This conclusion was not only confirmed by our updated IPDMA, but also extended by providing detailed information about the symptom-specific efficacy. As the effect on overall depression severity was small (effect size of .15), it is not surprising that the five identified symptom-specific effects were also small (effect sizes ranging from .13 to .16).

Small effects are, however, not uncommon in studies on the comparative efficacy of treatments. Given the robustness of the findings as well as the clinical relevance of the identified symptom-specific effects (especially the effect on "suicidal thoughts"), we believe that it would be unwise to ignore the beneficial effects of antidepressant medication over CBT.

Table 2 Improvements in depressive symptomatology in the ADM versus CBT condition

	ADM condition (N=570)	CBT condition (N=500)	p	Cohen's d
Overall depression severity (HAM-D total score, mean±SD)	10.49±6.84	9.43±6.87	0.01	.15
HAM-D scores for individual symptoms (mean±SD)				
Depressed mood	1.43±1.11	1.28±1.19	0.03	.13
Feelings of guilt	0.99±1.14	0.82±1.05	0.02	.16
Suicidal thoughts	0.60±1.04	0.44±0.97	0.007	.16
Early night insomnia	0.52±0.95	0.49±1.00	0.56	.03
Middle night insomnia	0.50±1.02	0.45±0.95	0.39	.05
Early morning insomnia	0.38±0.98	0.29±0.96	0.13	.09
Work and activities	1.53±1.29	1.39±1.33	0.08	.11
Retardation	0.40±0.67	0.36±0.76	0.32	.06
Agitation	0.35±0.97	0.37±0.97	0.68	–.02
Psychic anxiety	1.00±1.09	0.85±1.17	0.03	.13
Somatic anxiety	0.68±1.10	0.69±1.16	0.88	–.01
Gastrointestinal symptoms	0.32±0.78	0.29±0.71	0.47	.04
General somatic symptoms	0.75±0.92	0.64±0.83	0.05	.13
Genital symptoms	0.55±0.94	0.57±0.98	0.77	–.02
Hypochondriasis	0.29±0.84	0.32±0.94	0.67	–.03
Loss of weight	0.15±0.69	0.15±0.66	0.91	–.00
Insight	0.04±0.40	0.04±0.40	0.78	–.00

ADM – antidepressant medication, CBT – cognitive behavioral therapy, HAM-D – Hamilton Depression Rating Scale

To our knowledge, no previous RCTs have examined a broad spectrum of individual depressive symptoms in comparing the efficacy of antidepressant medication vs. CBT, but some have considered subscales based on combinations of symptoms[7-9]. None of these studies have found differences in the efficacy on cognitive and affective symptoms[7-9], although two identified short-term effects that disappeared at a later stage[7-8].

An explanation for the identified symptom-specific effects in our study could lie in the use of IPDMA, which, with its substantial statistical power, makes it possible to detect relatively small effects. In addition, the strategy of combining symptoms into subscale scores may have obscured differential responses at the level of individual symptoms. Fournier et al[9] found, for example, no differences between cognitive therapy and antidepressants on the "mood" subscale, which incorporates both symptoms that did (i.e., "depressed mood") and did not (i.e., "work and activities" and "retardation") differ between treatment conditions in our study. This combination of findings underlines the importance of sufficient statistical power as well as a focus on individual symptoms in research on treatment efficacy.

Although Fournier et al did not find any differences in subscales of cognitive and affective symptoms, they did find that cognitive therapy was more efficacious than medication in improving atypical-vegetative symptoms[9]. Additional analyses showed that this effect was only present for hypersomnia, but not increased appetite. It is important to note that these two atypical-vegetative symptoms are not included in the 17-item HAM-D and, thus, are not considered as outcomes in our study.

We believe that it would be important for future studies to also consider atypical-vegetative symptoms as well as other clinically relevant symptomatology (e.g., anxiety symptoms or alcohol problems). In addition, it would be interesting to consider other outcomes that are clinically relevant, such as various aspects of quality of life or daily functioning, in order to provide a more thorough evaluation of treatment options.

Direct and indirect symptom-specific effects of antidepressant medication vs. CBT

Our study used network estimation techniques to shed light on the mechanisms of change during treatment. These analyses revealed that four of the five symptom-specific effects were direct (i.e., "feelings of guilt", "suicidal thoughts", "psychic anxiety" and "general somatic symptoms") and, thus, were independent of any of the other direct or indirect symptom-specific effects of antidepressant medication over CBT. The effect on "depressed mood" was indirect, indicating that the larger improvement was only present in patients who also experienced larger improvements in other symptoms in the medication relative to CBT condition. It is, however, important to note that

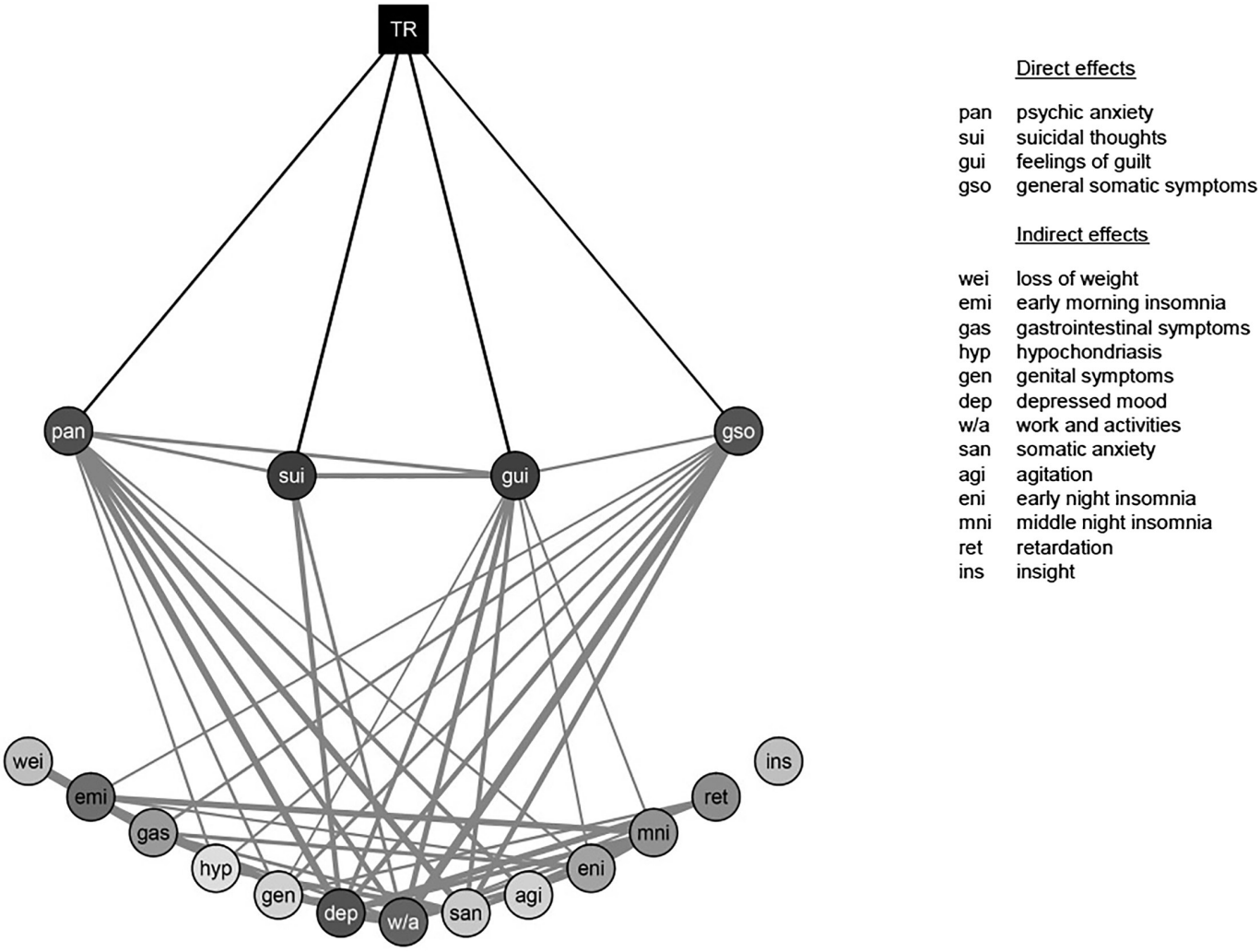

Figure 1 Direct and indirect symptom-specific effects of antidepressant medication (ADM) vs. cognitive behavioral therapy (CBT). Treatment type is represented by the square (TR), and individual symptoms as circles. Black lines indicate direct connections between treatment condition and improvements in individual symptoms (i.e., direct treatment effects), whereas grey lines indicate connections between improvements in individual symptoms (i.e., potential indirect treatment effects). Thicker lines represent stronger connections. Darker circles represent stronger effects of ADM over CBT. The network is presented at γ=0.25.

network estimations employ regularization techniques which set weak connections to zero and, thus, conservatively identify the most relevant connections. This implies that, in reality, antidepressant medication may have a weak direct effect on "depressed mood" and, thus, this effect would not be fully indirect. The same might be true for other connections in the network. Network estimations are, therefore, not intended to formally test for mediation, but do provide insights into the patterns in which symptom improvements are related and can be used in generating hypotheses.

The network further revealed that improvements in symptoms were related in very complex patterns, with connections that were often intuitively plausible. It is, for example, easy to imagine that patients reporting less depressed mood after treatment often also reported fewer problems with work and activities, whereas patients reporting fewer gastrointestinal symptoms often reported less loss of weight. Interestingly, the networks were similar for the two treatment conditions, indicating that, regardless of the treatment, patients tend to report the same simultaneous symptom improvements. The only difference between the treatment conditions, thus, lies in the magnitude of improvement of the five symptoms that were specifically affected by antidepressant medication over CBT.

Although our findings demonstrate potential in generating hypotheses regarding the mechanisms of change during treatment, it is important to remark that changes in symptoms were assessed simultaneously and, consequently, the temporal relationships between them remain unknown. To examine the actual dynamics of symptoms over time, it would be more appropriate to use experience sampling method data, including multiple assessments with short time intervals[37]. For such research, it would be valuable to also consider other clinically

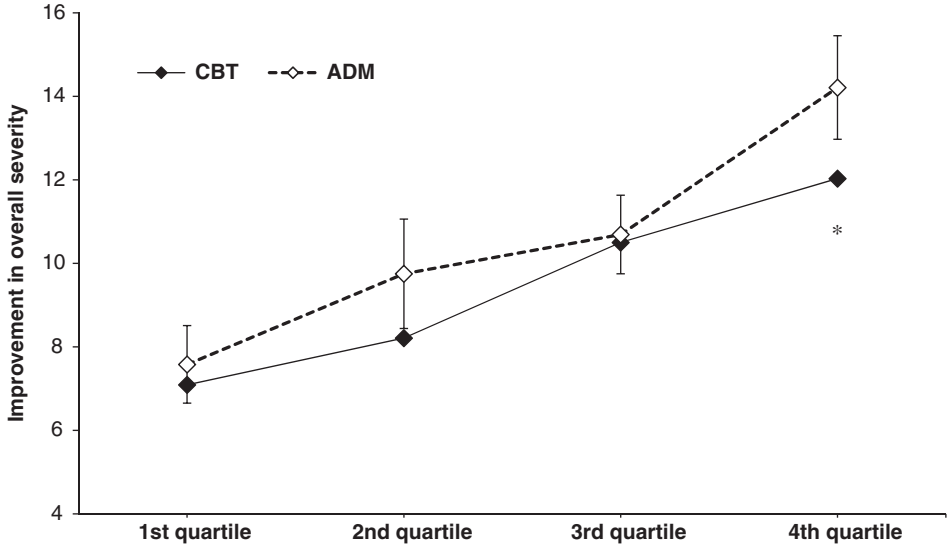

Figure 2 Stratification based on increasing scores on a specific pre-treatment severity indicator calculated by summing the five symptoms that responded the most to antidepressant medication (ADM) relative to cognitive behavioral therapy (CBT). * Cohen's d=.30.

relevant outcomes, as well as factors that are hypothesized to play a role in the working mechanisms of treatment, such as therapeutic alliance or social support.

Identifying patients who benefit more from antidepressant medication relative to CBT

Our findings showed that, in general, antidepressant medication was more efficacious than CBT in improving "depressed mood", "feelings of guilt", "suicidal thoughts", "psychic anxiety", and "general somatic symptoms" (effect sizes ranging from .13 to .16). This suggests that patients primarily suffering from these five symptoms would benefit more from antidepressant medication than from CBT, which was supported by our exploratory analyses. Only patients with the highest scores on these five symptoms showed significantly and substantially larger improvements in overall depression severity after medication relative to CBT (effect size of .30). In contrast, antidepressants and CBT were equally efficacious for patients with lower scores on these symptoms. Our findings, thus, may be an important step in "precision psychiatry", as they can inform clinicians more precisely about the preferred treatment option based on the pre-treatment symptomatology of a patient.

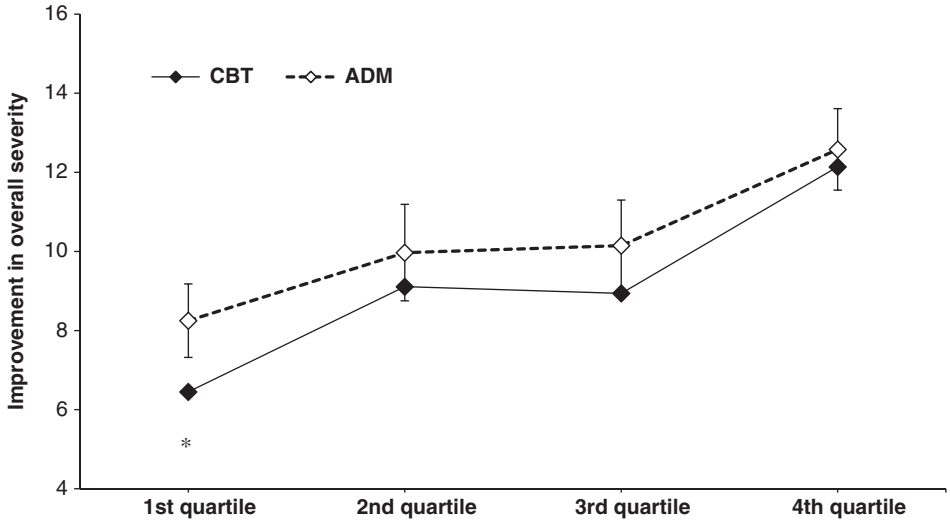

Figure 3 Stratification based on increasing scores on a specific pre-treatment severity indicator calculated by summing the five symptoms that responded the least to antidepressant medication (ADM) relative to cognitive behavioral therapy (CBT). * Cohen's d=.33.

Strengths and limitations

Strengths of the current study were that we used data from an updated IPDMA, which enabled us to assess treatment efficacy in more detail by focusing on individual symptoms. Although several studies have used network analysis techniques to examine the relations between depressive symptoms at a single time point[38-41], we were the first to use these techniques on changes in symptoms over time in order to distinguish direct and indirect treatment effects[13].

However, a focus on symptoms also brings challenges. For example, some studies have shown that the inter-rater reliability of several HAM-D items was poor[42], whereas others were more positive[43]. Therefore, more research is needed on the reliability and validity of assessing individual symptoms, especially as a measure of treatment efficacy. In addition, the number of response categories on the HAM-D differs across symptoms. Sensitivity to detect changes in symptom severity may be higher for symptoms with more response categories and this could explain the fact that, in general, the largest symptom-specific effects in our study, as well as in the study of Hieronymus et al[12], were observed for symptoms with more response categories.

The HAM-D items comprise a relatively narrow scope of possible outcomes and, therefore, it would be valuable to also consider other outcomes that are clinically relevant. It would also be interesting to consider other treatment options and to differentiate between antidepressant medication types, which are known to have different side effects[44].

CONCLUSIONS

Our study showed that antidepressant medication was more efficacious than CBT in improving five, but not twelve other, depressive symptoms. Although the five symptom-specific effects were small (effect sizes of .13 to .16), the specific symptoms, such as "suicidal thoughts", were all clinically relevant and, therefore, it would be unwise to ignore them. In addition, exploratory analyses suggested that this information could be helpful in "precision psychiatry": based on the pre-treatment symptomatology of patients, it was possible to identify those who were likely to benefit more from antidepressant medication than from CBT (effect size of .30) and those for whom both treatments were equally efficacious.

We think that such a symptom-oriented approach will be a step forward in research on treatment efficacy and we strongly encourage other researchers to adopt this approach in studies on other treatment options and/or to consider other outcomes.

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Transdiagnostic psychiatry: a systematic review

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The usefulness of current psychiatric classification, which is based on ICD/DSM categorical diagnoses, remains questionable. A promising alternative has been put forward as the "transdiagnostic" approach. This is expected to cut across existing categorical diagnoses and go beyond them, to improve the way we classify and treat mental disorders. This systematic review explores whether self-defining transdiagnostic research meets such high expectations. A multi-step Web of Science literature search was performed according to an a priori protocol, to identify all studies that used the word "transdiagnostic" in their title, up to May 5, 2018. Empirical variables which indexed core characteristics were extracted, complemented by a bibliometric and conceptual analysis. A total of 111 studies were included. Most studies were investigating interventions, followed by cognition and psychological processes, and neuroscientific topics. Their samples ranged from 15 to 91,199 (median 148) participants, with a mean age from 10 to more than 60 (median 33) years. There were several methodological inconsistencies relating to the definition of the gold standard (DSM/ICD diagnoses), of the outcome measures and of the transdiagnostic approach. The quality of the studies was generally low and only a few findings were externally replicated. The majority of studies tested transdiagnostic features cutting across different diagnoses, and only a few tested new classification systems beyond the existing diagnoses. About one fifth of the studies were not transdiagnostic at all, because they investigated symptoms and not disorders, a single disorder, or because there was no diagnostic information. The bibliometric analysis revealed that transdiagnostic research largely restricted its focus to anxiety and depressive disorders. The conceptual analysis showed that transdiagnostic research is grounded more on rediscoveries than on true innovations, and that it is affected by some conceptual biases. To date, transdiagnostic approaches have not delivered a credible paradigm shift that can impact classification and clinical care. Practical "TRANSD"iagnostic recommendations are proposed here to guide future research in this field.

Key words: Transdiagnostic, diagnosis, classification, bibliometric analysis, conceptual analysis, anxiety, depression, psychosis, recommendations

(World Psychiatry 2019;18:192–207)

Diagnosis, which is the medical application of the process of classification, ubiquitous in science, has been the cornerstone of modern clinical knowledge and practice[1]. Diagnosis in psychiatry started in Europe in the late 17th century, informed by systems that classified animal and plant species as part of other natural sciences[2]. Psychiatric nosology, traditionally represented by the ICD and DSM (gold standard), is based on categorical diagnoses that are intertwined with the key clinical dichotomies that characterize the realm of clinical medicine (e.g., to treat or not to treat)[3,4].

Since its inception, psychiatric nosology has always been under fire. This is documented by several lines of evidence, including two recent issues of this journal[3,5]. Although current diagnostic categories have demonstrated moderate to almost perfect reliability[6], their usefulness has remained questionable[7].

A promising avenue has been put forward by the so-called transdiagnostic approach. The prefix "trans" comes from Latin and it can either mean across/through (e.g., transatlantic) or beyond (e.g., transcend)[8]. Therefore, a transdiagnostic approach in psychiatry is expected to cut across existing categorical diagnoses and go beyond them, to produce a better classification system, compared to the existing gold standard.

Transdiagnostic approaches originated from cognitive behavioral theories and treatments for eating disorders[9,10], which were then extended to anxiety[11-13] and depressive disorders[14]. The initial transdiagnostic rationale leveraged two core points: a) these disorders share common etiological and maintenance processes[9,10,13,15] as well as cognitive-affective, interpersonal, and behavioral features[9,10,15] (e.g., the general psychopathology latent factor – p factor[16]), and b) the ever-growing number of disorder-specific treatment manuals is a barrier to the implementation of cognitive behavioral treatments[10,13,15].

The rationale for extending the transdiagnostic paradigm to anxiety and depressive disorders included an additional point that was not originally acknowledged[10]: c) disorder-specific interventions rely on heterogeneous diagnostic categories and pay relatively limited attention to comorbidity, which is high[15].

Transdiagnostic research aims at tackling these limitations to introduce a novel approach that could improve the way we classify, formulate, treat, and prevent[15] mental disorders. Moving away from a single-diagnosis approach towards a transdiagnostic conceptualization and treatment of mental disorders would thus be a significant paradigm shift[15]. Recently, transdiagnostic approaches have been endorsed by other paradigms that cut across different mental disorders, such as the Research Domain Criteria (RDoC) initiative[17] and the clinical staging model[18]. At present, however, it is unclear whether transdiagnostic research meets such high expectations for delivering a radical paradigm shift that impacts classification and clinical care.

To address this issue, we present here a broad systematic review of transdiagnostic research in psychiatry. We systematically assess the transdiagnostic literature against several

empirical variables which index core characteristics as well as potential pitfalls. A bibliometric and conceptual analysis complements the empirical findings, along with practical recommendations to guide future research in this field.

METHODS

The PRISMA compliant[19] protocol for this study was registered on PROSPERO (CRD42018108613).

Search strategy, selection criteria and data extraction

A multi-step literature search was performed. First, systematic searches were conducted in the Web of Science (which includes Web of Science Core Collection, BIOSIS Citation Index, KCI - Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index), until May 5, 2018, with no restrictions on language or publication date. The keyword "transdiagnostic" was used, filtering for the category "psychiatry" through the Web of Science categories function. Second, we searched the reference lists of retrieved articles. Third, abstracts identified by this process were then screened and full-text articles were inspected against the inclusion and exclusion criteria.

The literature search, study selection and data extraction were conducted by two authors (MS, NB) independently. During all stages, in the case of disagreement, consensus was reached through discussion with a third author (PFP).

Studies were eligible for inclusion when the following criteria were fulfilled: a) original individual articles, with no restriction on study design (including interventional and observational studies) or topic; b) a clear and primary focus on a transdiagnostic approach, demonstrated by using the word "transdiagnostic" in the title.

The exclusion criteria were: a) reviews, meta-analyses, study protocols, abstracts and any other non-original data; b) lacking a clear primary focus on transdiagnostic approaches, defined as above; and c) studies with less than ten participants[20].

Descriptive variables

For each study, we extracted descriptive variables relating to: a) general information, b) definition of gold standard diagnostic criteria, c) outcome measures, d) definition of the transdiagnostic approach, and e) quality assessment.

General information variables included: first author and year of publication; study domain (classification, treatment, clinical prediction, neuroscience, cognition and psychological processes); study design (observational, uncontrolled interventional, controlled interventional); type of design (cross-sectional, longitudinal, unrandomized, randomized); total sample size (total pool of participants recruited at baseline, including non-clinical samples); and mean age (or age range).

Variables relating to the definition of the gold standard diagnostic criteria included: whether the study explicitly acknowledged the type of gold standard used (DSM or ICD, any version); the specific type of primary diagnoses of mental disorders and their specific ICD or DSM codes; the presence of any other clinical condition as defined by each individual study; the presence of a non-clinical sample (e.g., healthy controls); the total number of ICD/DSM mental disorders investigated by the study; the total number of diagnostic spectra (defined according to the ICD-10 diagnostic blocks: organic, including symptomatic 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 physiological disturbances and physical factors; disorders of adult personality and behavior; mental retardation; disorders of psychological development; behavioral and emotional disorders with onset usually occurring in childhood and adolescence; unspecified mental disorders); and the type of psychometric instrument employed to define the gold standard.

Variables relating to the outcomes included: whether the primary outcome of the study was clearly acknowledged in the manuscript; the specific type of instruments employed to define it; and the total number of primary outcomes.

Variables relating to the transdiagnostic approach included: the exact definition of the transdiagnostic construct as provided by each study; the number of transdiagnostic constructs (single or multiple)[21]; whether the transdiagnostic construct was descriptive (a construct which is present in multiple disorders, without regard to how or why[22]) or mechanistic (a construct that may reflect an underlying physiological, neurobiological or functional mechanism[22]); whether the construct was causally associated with the outcome (to rule out the possibility that a construct may just be epiphenomenal[21]); whether the transdiagnostic construct was present in all clinical conditions and spectra (universal transdiagnostic process) and in how many of them. We also extracted the type of statistical analysis used to probe the transdiagnostic construct; whether there was a formal statistical assessment of the impact of the transdiagnostic approach compared to the specific-diagnostic approach; and the results of such a test.

Quality assessment was performed by recording if an *a priori* protocol had been made available, if funding was provided by industry, and if the core findings had been externally replicated in an independent sample.

Analysis

The descriptive variables were used to perform different types of analyses.

First, descriptive summary data and statistics (i.e., frequencies, means/medians, ranges) of the above variables were narratively presented in the text and in informative tables.

Second, each study was assessed against the criteria introduced by Mansell et al[21] to define transdiagnostic approaches

in psychiatry: a) presence of a clinical population, b) presence of at least four different mental disorders, c) presence of a non-clinical sample, and d) demonstration of the transdiagnostic construct in all mental disorders investigated.

Third, the conceptual definition of the transdiagnostic approach was empirically deconstructed. The main aim was to explore the extent to which each transdiagnostic approach related to the existing diagnostic categorical system. As indicated in Figure 1, the simplest transdiagnostic approach – defined as "across-diagnoses" – was to compare different ICD/DSM categorical diagnoses against each other, to test their diagnostic boundaries and cross-cutting features. The across-diagnoses model could include one diagnostic spectrum, multiple spectra and/or non-clinical samples, including also healthy individuals. A more elaborated approach involved the definition of new diagnostic-like constructs, for example based on biotypes or clinical types, and then testing the relatedness of these newly defined constructs against the gold standard. These approaches were termed "beyond-diagnoses", because they employed standard ICD/DSM diagnostic information but went beyond it, to test new diagnostic constructs. When studies did not fit within any of the above two categories, the specific approach was described.

Fourth, we conducted a bibliometric analysis using the list of specific ICD/DSM mental disorders that were analyzed by each study (when available). These data were then loaded into R software and cleaned with the Bibliometrix and TM packages. The processed data were then loaded into Gephi software to generate the network map of the specific ICD/DSM mental disorders investigated by transdiagnostic research. Each node indicated a specific mental disorder, with the node's size reflecting how many different connections (frequency) with other nodes were present. The thickness of the edges reflected the number of connections between a pair of nodes/mental disorders. For graphical purposes, nodes that had frequency ≤6 and number of co-occurrent connections ≤3 were filtered out.

RESULTS

Studies identified

The literature search identified 627 potential records that were screened on the basis of title and abstract reading. Of these, 239 were considered eligible for full screening. At this stage, 128 studies were further excluded, leaving a sample of 111 studies, which represented the final database for the current systematic review (Figure 2).

Characteristics of transdiagnostic studies in psychiatry

General information

The first study, published in 2004 by Norton et al[11], addressed the effects of a transdiagnostic psychological intervention for different types of anxiety disorders. Since then, there was one study published in 2006, six in 2008, four in 2009, six in 2012, six in 2013, thirteen in 2014, eleven in 2015, eighteen in 2016, thirty-four in 2017, and eleven up to May 2018.

Most studies (45%) were investigating interventions (of which 50% were controlled, 48% uncontrolled[23-46], and 2% unclear[47]). Less than half (46%)[11,43,48-68] of the interventional studies were randomized. All interventional studies focused on neurotic, stress-related and somatoform disorders or mood (affective) disorders, while other mental disorders were rarely investigated (Table 1).

Cognition and psychological processes was the second most frequent topic (28%), followed by neuroscientific topics

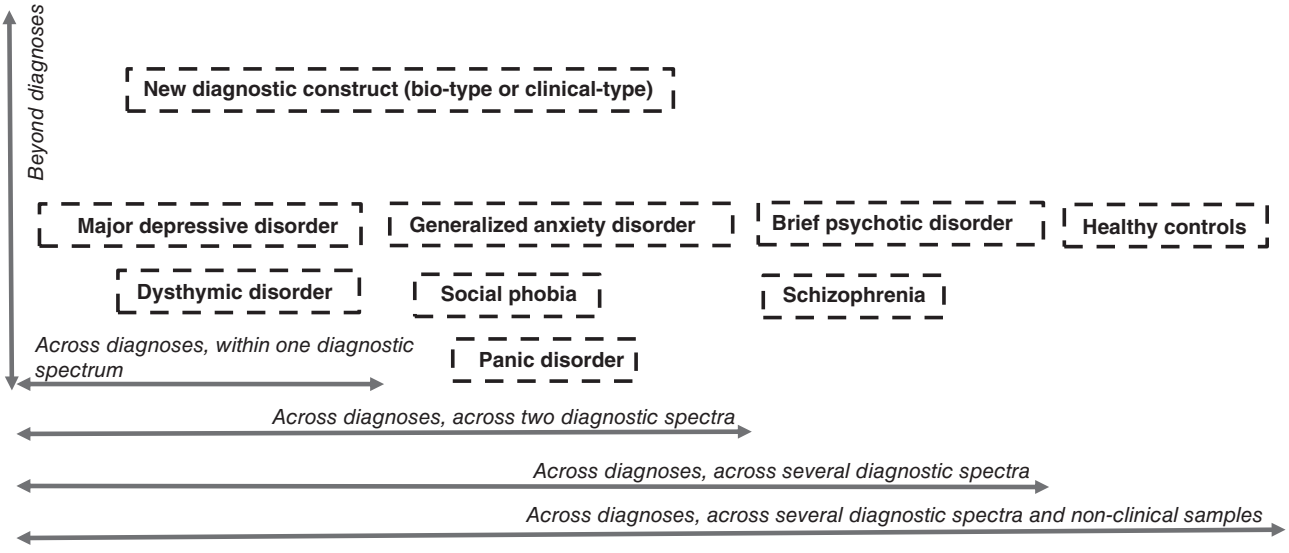

Figure 1 Conceptual classification of transdiagnostic approaches most widely employed in psychiatry, with some prototypical diagnostic examples

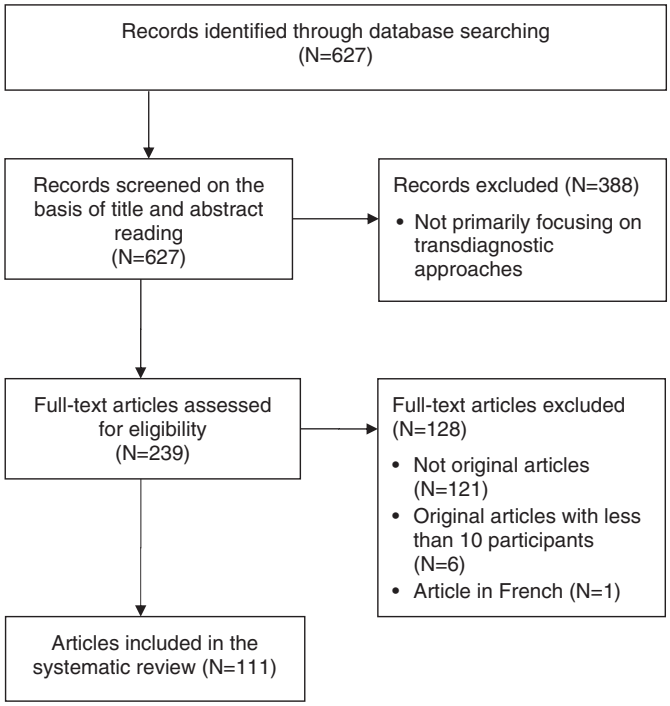

Figure 2 Study identification and selection (PRISMA flow chart)

(13%). Classification and prediction studies were more infrequent (4% and 10% respectively) (Table 1).

The vast majority of non-interventional studies (79%) were cross-sectional, and only 21%[69-81] longitudinal. There was a large variability in study sample size, ranging from 15 participants in the smallest study[42] to 91,199 in the largest[73] (median: 148 participants). The mean age of individuals (when available) ranged from 10[44] to more than 60[23] (median: 33 years).

Definition of gold standard diagnostic criteria

A substantial proportion (27%) of studies[24,29,36,40,48,49,64,69-71,73,78,80,82-98] did not acknowledge using any psychometric interview to establish their gold standard diagnoses. Several studies (16%)[29,34,54,70,71,78,82,83,85-88,92,93,95,97,99,100] did not refer to a gold standard diagnostic manual, but speculated on comparative benefits of the transdiagnostic approach over specific diagnoses[29,71].

Some studies reported non-existent (e.g., DSM-IV-TR bipolar II disorder with psychotic features[84]) or incorrect diagnoses (e.g., suicidality[34], marijuana abuse/dependence[76,101], late onset schizophrenia-like psychosis[100], social anxiety disorder and social phobia as two distinct DSM-IV disorders[101]). Other studies included health anxiety within mental disorders, confusingly defined either as not relating to a specific diagnosis[90], as hypocondriasis[23], or as "health-based anxiety predominant in individuals with illness anxiety disorders and somatic symptom disorders"[90].

One interventional study stated that the participants were not diagnosed at all[88]. The study addressed this issue by simply noting that "it would have been informative to know client diagnoses"[88], raising concerns about unnecessary or excessive treatments in this sample[102].

Some studies used comorbid (as opposed to primary) diagnoses to validate the transdiagnostic construct[50,52,56,59-63,99,103]. In about one third of studies (28%)[34,36,54,69,70,72,74,75,82,85,87,89,104-107], the boundaries between primary and secondary diagnoses were not completely clear.

There was also some confusion between the measurement of symptoms as opposed to categorical disorders. This was mainly due to the use of continuous measurements that were not translated into ICD/DSM diagnostic categories through the use of *a priori* cut-offs[83]. Three studies measured DSM-related items in non-clinical samples without applying cut-offs to establish the intake of specific diagnostic categories[86,90,91]. The results were there interpreted in the context of the disorder-oriented literature[91], arguing that findings were related to specific categorical diagnoses[86,90]. These studies concurrently acknowledged a transdiagnostic approach in their title – as for any other study included in the current review – and "the lack of diagnostic measures" in the study itself[91].

An interventional study which did not use cut-offs to define post-traumatic stress disorder concluded that treating distress was better than treating the categorical disorder[29]. Another interventional study which measured symptoms but not disorders tautologically concluded that the potential advantage of transdiagnostic interventions was a reduced need for disorder-based assessments[88]. Some studies did apply cut-offs but eventually did not use them for their main analyses[48,94].

Frequently, studies did not specify the exact ICD/DSM types of mental disorders that were investigated, but only referred to the general domains of psychotic disorders[34,106], substance induced disorders[28,34,108], anxiety disorders[23,28,54,88,93,104], mood disorders[23,28,48,49,54,64,88,93], or mood and anxiety disorders[54,93]. The specific ICD/DSM diagnostic codes were hardly ever reported.

The number of primary mental disorders investigated by each study was highly variable and overall relatively low, ranging from no evidence of mental disorders at all (13% of studies)[24,29,70,78,82,85-88,90-92,95,97] and one mental disorder (8% of studies)[50,59-63,96,109,110], up to 353 mental disorders[73] (median: four mental disorders per study). Similarly, the number of ICD-defined diagnostic spectra was heterogeneous, ranging from zero (12% of studies)[29,70,78,82,85-88,90-92,95,97] to ten[73] (median: one spectrum) per study. The largest transdiagnostic study published to date leveraged an electronic case register to include 353 mental disorders clustered across ten spectra, representing all ICD-10 mental disorders except organic mental disorders[73]. About one third of the studies (35%)[29,40,70,74,76,78,81,82,85-87,90-92,94-98,100,101,103,105-107,111-124] included at least one non-clinical sample.

Outcome measures

Only a minority (35%)[23-25,32,34-36,40,48,49,51-53,56-62,64,66-68,73,74,83,84,88,100,103,111,112,115,125-128] of studies explicitly acknowledged

Table 1 Studies included in the systematic review

Study	Year	Domain	Baseline N	Mean age	Gold standard	Transdiagnostic construct	Transdiagnostic type	Mansell criteria
Van Dijk et al[23]	2018	Treatment	53 and 64	>60	DSM-IV-TR	Psychotherapeutic day treatment and activating day treatment	Across diagnoses, across spectra	No
Samtani et al[109]	2018	Prediction	183	23	DSM-IV	Repetitive negative thinking	Within the same diagnosis	No
Pellizzer et al[69]	2018	Prediction	78	27	DSM-5	Body image flexibility	Across diagnoses, within spectrum	No
Nota & Coles[104]	2018	Neuroscience	52	36	DSM-IV-TR	Repetitive negative thinking	Across diagnoses, across spectra	No
McEvoy et al[82]	2018	Prediction	2,088	20	NA	Repetitive negative thinking	A-diagnostic	No
Grisanzio et al[111]	2018	Classification	420	40	DSM-IV	Subtypes based on neuro-cognition, brain activation and functional capacity	Beyond diagnoses	No
Goldschmidt et al[125]	2018	Classification	636	15	DSM-5	Eating disorders symptoms network	Across diagnoses, within spectrum	No
Dear et al[24]	2018	Treatment	28	41	DSM-IV	Cognitive behavioral therapy	Across physical and mental health diagnoses	No
Curzio et al[129]	2018	C&P processes	419	15	DSM-IV-TR	Binge eating, dietary restrain, affective, interpersonal problems and perfectionism	Across diagnoses, within spectrum	No
Ciaramidaro et al[105]	2018	Neuroscience	78	22	ICD-10	Facial recognition	Across diagnoses, across spectra and non-clinical samples	No
Capobianco et al[48]	2018	Treatment	40	28	DSM-IV	Metacognitive and mindfulness meditation therapies	Across diagnoses, across spectra	No
Zwerenz et al[49]	2017	Treatment	82	40	ICD-10	Psychodynamic web-based self-help intervention	Across diagnoses, across spectra	No
Zemestani et al[50]	2017	Treatment	43	23	DSM-IV	Cognitive behavioral therapy	Within the same diagnosis	No
Wigman et al[70]	2017	C&P processes	293	19	NA	Interconnectedness of psychotic and affective experiences	A-diagnostic	No
Talkovsky et al[25]	2017	Treatment	129	33	DSM-IV-TR	Group cognitive behavioral therapy	Across diagnoses, within spectrum	No
Talkovsky et al[26]	2017	Treatment	120	33	DSM-IV-TR	Group cognitive behavioral therapy	Across diagnoses, within spectrum	No
Smith et al[27]	2017	Treatment	49	33	DSM-IV	Anxiety symptoms questionnaire	Across diagnoses, within spectrum	No
Shinn et al[71]	2017	Classification	91	21	NA	Clinical service	Across diagnoses, across spectra	No
Sheffield et al[112]	2017	Neuroscience	576	35	DSM-IV	Functional brain network integrity	Across diagnoses, across spectra and non-clinical samples	No
Sharma et al[51]	2017	Treatment	63	14	ICD-10	Group cognitive behavioral therapy	Across physical and mental health diagnoses	No
Schroder et al[52]	2017	Treatment	179	37	DSM-IV	Internet intervention	Across diagnoses, within spectrum	No
Riccardi et al[53]	2017	Treatment	28	29	DSM-IV	False safety behavior elimination therapy	Across diagnoses, within spectrum	No
Platt et al[72]	2017	Prediction	4,925	13-18	DSM-IV	Timing of menarche and internalizing factors	Across diagnoses, across spectra	No
Pitman et al[28]	2017	Treatment	73	29	DSM-IV	Short-term psychodynamic psychotherapy	Across diagnoses, across spectra	No

Table 1 Studies included in the systematic review (*continued*)

Study	Year	Domain	Baseline N	Mean age	Gold standard	Transdiagnostic construct	Transdiagnostic type	Mansell criteria
Newby et al[83]	2017	Treatment	2,109	40	DSM-IV	Internet-based cognitive behavioral therapy	Across diagnoses, across spectra	No
Maia et al[54]	2017	Treatment	67	>18	DSM-IV, ICD-10	Cognitive behavioral therapy	Across diagnoses, across spectra	No
MacNamara et al[113]	2017	Neuroscience	199	26	DSM-IV	Affective face processing	Across diagnoses, across spectra and non-clinical samples	No
Lee et al[84]	2017	Prediction	163	20	DSM-IV-TR	Neuropsychological functioning	Across diagnoses, across spectra	No
LeBouthillier & Asmundson[55]	2017	Treatment	48	33	DSM-5	Aerobic exercise and resistance training	Across diagnoses, within spectrum	No
Keil et al[114]	2017	C&P processes	108	12	DSM-5	Emotions regulation	Across diagnoses, across spectra and non-clinical samples	No
Jauhar et al[115]	2017	Neuroscience	60	24	DSM-IV	Dopamine synthesis capacity	Across diagnoses, across spectra and non-clinical samples	No
Hankin et al[85]	2017	C&P processes	1,125	11	NA	Temperamental and psychopathology factors	A-diagnostic	No
Hamblen et al[29]	2017	Treatment	342	57	NA	Cognitive behavioral therapy	Across symptoms	No
Gros et al[30]	2017	Treatment	16	47	DSM-5	Cognitive behavioral therapy	Across diagnoses, across spectra	No
Gong et al[116]	2017	Neuroscience	272	34	DSM-IV	Intra/inter-network connectivity	Across diagnoses, across spectra and non-clinical samples	No
Gibson et al[86]	2017	C&P processes	2,342	21	NA	Exposure to traumatic life events	Across symptoms	No
Fusar-Poli et al[73]	2017	Prediction	91,199	33	CAARMS, ICD-10	Risk model of transition to psychosis	Across diagnoses, across spectra	No
Forbush et al[126]	2017	Classification	207	25	DSM-5	Distress and fear-avoidance internalizing factors	Beyond diagnoses	No
Feldker et al[117]	2017	Neuroscience	134	28	DSM-IV	Brain response to visual threat	Across diagnoses, within spectrum and non-clinical samples	Yes
Espejo et al[31]	2017	Treatment	48	45	DSM-IV	Group cognitive behavioral therapy	Across diagnoses, within spectrum	No
Ellard et al[56]	2017	Treatment	29	44	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
Chen et al[118]	2017	Neuroscience	60	41	DSM-IV	Functional connectivity density	Across diagnoses, across spectra and non-clinical samples	No
Chasson et al[87]	2017	C&P processes	3,094	15	NA	Emotional vulnerabilities	A-diagnostic	No
Berger et al[57]	2017	Treatment	139	42	DSM-IV	Internet-based cognitive behavioral therapy	Across diagnoses, within spectrum	No
Barlow et al[58]	2017	Treatment	233	31	DSM-IV, DSM-5	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
Talkovsky & Norton[32]	2016	Treatment	151	33	DSM-IV	Group cognitive behavioral therapy	Across diagnoses, within spectrum	No
Sunderland et al[119]	2016	C&P processes	8,871	16-85	DSM-IV	Two factor internalizing-substance dependence model	Across diagnoses, across spectra and non-clinical samples	No
Stanton et al[106]	2016	C&P processes	299	47	DSM-5	Emotion regulation and basic personality dimensions	Across diagnoses, across spectra and non-clinical samples	No

Table 1 Studies included in the systematic review (*continued*)

Study	Year	Domain	Baseline N	Mean age	Gold standard	Transdiagnostic construct	Transdiagnostic type	Mansell criteria
Sabharwal et al[108]	2016	Neuroscience	82	45	DSM-IV	Behavioral and neural measures of emotion-related working memory	Across diagnoses, across spectra	No
Reininghaus et al[130]	2016	Classification	1,168	42	RDoC	Bifactor model with general and specific psychosis dimensions	Beyond diagnoses	No
Philip et al[74]	2016	Prediction/ neuroscience	46	39	DSM-IV-TR	Thalamic connectivity in early life stress	Across diagnoses, across spectra and non-clinical samples	No
Morris et al[88]	2016	Treatment	108	41	NA	Group based psychological intervention	Across symptoms	No
McIntosh et al[59]	2016	Treatment	112	35	DSM-IV	Cognitive behavioral therapy	Within the same diagnosis	No
McEvoy & Erceg-Hurn[33]	2016	Treatment	256	34	DSM-IV	Intolerance of uncertainty	Across diagnoses, across spectra	No
Kristjánsdóttir et al[34]	2015	Treatment	287	39	DSM-IV, ICD-10	Group cognitive behavioral therapy	Across diagnoses, across spectra	No
Ito et al[35]	2016	Treatment	28	35	DSM-IV	Cognitive behavioral therapy	Across diagnoses, across spectra	No
Holliday et al[89]	2016	C&P processes	783	29	DSM-5	Distress tolerance	Across diagnoses, across spectra	No
Hadjistavropoulos et al[36]	2016	Treatment	458	39	DSM-IV	Internet-based cognitive behavioral therapy	Across diagnoses, across spectra	No
Fogliati et al[60]	2016	Treatment	145	41	DSM-IV	Cognitive behavioral therapy	Within the same diagnosis	No
Dear et al[61]	2016	Treatment	233	42	DSM-IV	Cognitive behavioral therapy	Within the same diagnosis	No
Conway et al[75]	2016	C&P processes	815	15	DSM-IV	Internalizing and externalizing factors mediating appraisal biases	Transdiagnostic outcome	No
Conway et al[107]	2016	Prediction	700	20	DSM-IV	Latent model of personality disorder	Across diagnoses, across spectra and non-clinical samples	No
Asnaani et al[37]	2016	Treatment	107	33	DSM-5	Anxiety sensitivity, depression, rumination as moderators of cognitive behavioral therapy	Across diagnoses, within spectrum	No
Titov et al[62]	2015	Treatment	290	44	DSM-IV	Cognitive behavioral therapy	Within the same diagnosis	No
Thibodeau et al[90]	2015	C&P processes	1,255	22	DSM-IV-TR	Intolerance of uncertainty	Across symptoms	No
Tang-Smith et al[91]	2015	C&P processes	612	21	DSM-III	Dominance behavioral system	Across symptoms	No
Rodriguez-Seijas et al[127]	2015	C&P processes	5,191	NA	DSM-IV	Internalizing and externalizing factors	Across diagnoses, across spectra	No
Pietrzak et al[110]	2015	C&P processes	267	54	DSM-IV	Loss symptoms, threat symptoms and somatic symptoms	Within the same diagnosis	No
Maia et al[99]	2015	Treatment	48	18-58	DSM-IV, ICD-10	Cognitive behavioral therapy	Across diagnoses, across spectra	No
Latack et al[76]	2015	C&P processes	34,653	>18	DSM-IV	Internalizing and externalizing factors	Across diagnoses, across spectra and non-clinical samples	No
Hsu et al[131]	2015	C&P processes	51	33	DSM-IV	Self-reported attentional control and rumination	Across diagnoses, across spectra	No

Table 1 Studies included in the systematic review (*continued*)

Study	Year	Domain	Baseline N	Mean age	Gold standard	Transdiagnostic construct	Transdiagnostic type	Mansell criteria
Dear et al[63]	2015	Treatment	366	44	DSM-IV	Cognitive behavioral therapy	Within the same diagnosis	No
Corral-Frías et al[101]	2015	Neuroscience	906	20	DSM-IV	Ventral striatal reactivity to reward	Across diagnoses, across spectra and non-clinical samples	No
Bedwell et al[120]	2015	Neuroscience	48	36	DSM-IV	Visual evoked potentials	Across diagnoses, across spectra and non-clinical samples	No
Vann et al[128]	2014	C&P processes	27	26	DSM-IV-TR	Metacognitions	Across diagnoses, within spectrum	No
Talkovsky & Norton[38]	2014	Treatment	256	33	DSM-IV	Negative affectivity, anxiety sensitivity, intolerance uncertainty	Across diagnoses, within spectrum	No
Starr et al[77]	2014	Prediction	1,630	28	DSM-IV	Latent internalizing factors for psychopathology	Transdiagnostic outcome	No
Spielberg et al[121]	2014	Neuroscience	179	27	DSM-IV	Dimensions of anxiety and depression	Across diagnoses, across spectra and non-clinical samples	No
Queen et al[39]	2014	Treatment	59	15	DSM-IV	Cognitive behavioral therapy	Across diagnoses, across spectra	No
Pietrzak et al[103]	2014	Neuroscience	35	29	DSM-IV-TR	Threat and loss symptoms	Across diagnoses, across spectra and non-clinical samples	No
Newby et al[40]	2014	Treatment	707	40	DSM-IV	Internet-based cognitive behavioral therapy	Across diagnoses, across spectra and non-clinical samples	No
McLaughlin et al[78]	2014	Prediction	1,065	12	NA	Rumination	A-diagnostic	No
McEvoy et al[122]	2014	C&P processes	786	28	DSM-IV	Repetitive negative thinking	Across diagnoses, across spectra and non-clinical samples	No
Gros[41]	2014	Treatment	29	50	DSM-IV	Cognitive behavioral therapy	Across diagnoses, across spectra	No
Cameron et al[92]	2014	C&P processes	41	28	NA	Emotion perception and semantic memory	A-diagnostic	No
Bullis et al[42]	2014	Treatment	15	32	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
Bohnke et al[93]	2014	C&P processes	11,939	38	DSM-IV	Negative affectivity	Across diagnoses, across spectra	No
Norton et al[47]	2013	Treatment	79	33	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
McEvoy et al[132]	2013	C&P processes	513	37	DSM-IV	Repetitive negative thinking	Across diagnoses, across spectra	No
McEvoy & Mahoney[133]	2013	C&P processes	99	NA	DSM-IV	Intolerance of uncertainty and negative metacognitive beliefs	Across diagnoses, within spectrum	No
Johnson et al[94]	2013	C&P processes	334	19	DSM-IV	Impulsive responses to emotion	Across diagnoses, across spectra and non-clinical samples	No
Ebert et al[64]	2013	Treatment	400	45	ICD-10	Internet-based maintenance treatment	Across diagnoses, across spectra	No
Boswell et al[43]	2013	Treatment	54	30	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
Norton & Barrera[65]	2012	Treatment	46	31	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No

Table 1 Studies included in the systematic review (*continued*)

Study	Year	Domain	Baseline N	Mean age	Gold standard	Transdiagnostic construct	Transdiagnostic type	Mansell criteria
Norton[66]	2012	Treatment	87	33	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
Hoiles et al[95]	2012	C&P processes	224	31	NA	Cognitive model for eating disorder	A-diagnostic	No
Farchione et al[67]	2012	Treatment	37	29	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
Conway et al[79]	2012	C&P processes	815	15	DSM-IV	Internalizing and externalizing factors	Across diagnoses, across spectra	No
Bilek & Ehrenreich-May[44]	2012	Treatment	22	10	DSM-IV	Group cognitive behavioral therapy	Across diagnoses, within spectrum	No
Innis et al[96]	2009	Neuroscience	135	28	DSM-IV	Homocysteine remethylation	Within the same diagnosis	No
Hagenaars et al[123]	2009	C&P processes	252	29	DSM-IV	Trauma and panic memories	Across diagnoses, within spectrum and non-clinical samples	No
Fairburn et al[68]	2009	Treatment	154	26	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
Bentall et al[100]	2009	C&P processes	237	53	DSM-IV, ICD-10	Paranoia, cognitive performance and depressive style	Across diagnoses, across spectra and non-clinical samples	Yes
Norton et al[46]	2008	Treatment	54	32	DSM-IV	Group cognitive behavioral therapy	Across diagnoses, within spectrum	No
Norton[45]	2008	Treatment	52	33	DSM-IV	Group cognitive behavioral therapy	Across diagnoses, within spectrum	No
McFarlane et al[80]	2008	Prediction	58	30	DSM-IV	Predictors of relapse	Across diagnoses, within spectrum	No
Corcoran et al[124]	2008	C&P processes	148	38	DSM-IV	Theory of mind and jumping to conclusions	Across diagnoses, across spectra and non-clinical samples	No
Brown et al[97]	2008	C&P processes	38	20	NA	Measure of mundane meaning	A-diagnostic	No
Bentall et al[98]	2008	C&P processes	148	38	DSM-IV	Negative self-esteem and negative expectations	Across diagnoses, across spectra and non-clinical samples	Yes
Wade et al[81]	2006	C&P processes	1,002	35	DSM-IV	Dimensional model of eating disorders	Across diagnoses, across spectra and non-clinical samples	No
Norton et al[11]	2004	treatment	23	>19	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No

C&P processes – cognition and psychological processes, CAARMS – Comprehensive Assessment of At Risk Mental State, RDoC – Research Domain Criteria, NA – not available

their primary outcome measure, which may be suggestive of suboptimal study quality. There was also a high variability in the number of primary outcome measures, ranging from one[48] to thirteen[81] (median: two measures) per study.

Definition of the transdiagnostic approach

The exact definition of the transdiagnostic construct per study is provided in Table 1. Only a minority of constructs (36%) involved multiple processes[28,37,38,48,55,59,70,72,75-77,79,80,85,87,91,92,96,98,100,103,106,110,111,113,114,116,119-121,123-132]. Most studies (81%) were descriptive in nature. Mechanistic constructs were more infrequent (19%)[28,32,38,48,50-53,58,70,83,103,112-118,131,133], and causal transdiagnostic constructs were hardly ever reported (7%)[24,48,50-53,58,115] and only during the most recent years (2017-2018).

The transdiagnostic construct was demonstrated across all clinical conditions investigated only in a minority (34%) of studies[24,27,30,32,38,42,43,45,47,50,52,53,57,58,60-63,65,71,80,83,89,96,98,109-

[113,115,117,118,123,128-130,133]. It was demonstrated in a median of three conditions and one spectrum. Several studies did not clarify at all whether the construct was present in the conditions investigated. Overall, no clear universal transdiagnostic construct that could be valid across all mental disorders and diagnostic spectra was identified.

The statistical methods used to test the impact of the transdiagnostic construct encompassed analysis of variance/covariance, correlations, regressions and general linear models, mixed effect models, moderation and mediation analysis, principal component analysis, structural equation modelling, network analysis, and machine learning.

Less than half (44%) of the studies[27,33,38,58,60,61,65,72-75,77,79-81,83,84,89,93,98,100,101,103,105,107-109,111-121,123-133] performed a statistical comparative assessment of the transdiagnostic approach versus a specific-diagnostic approach. This problem was particularly relevant for interventional studies, half of which lacked a comparative specific-diagnostic group. Overall, only 16% of them[27,33,38,58,60,61,65,83] performed a statistical comparative assessment. Some of these studies acknowledged that reliable conclusions regarding the diagnostic specificity of the findings could not be drawn[34,64]. However, other interventional studies lacking both a control group and statistical comparative assessment eventually (over)stated that the transdiagnostic cognitive behavioral treatment was effective in improving outcomes[40] or that it was more effective than the specific-diagnostic approach[29]. When comparative analyses were available, they generally indicated similar effects of the transdiagnostic vs. the specific-diagnostic intervention[58,60,61,83].

The qualitative appraisal of the transdiagnostic vs. specific-diagnostic effects – when available – revealed further inconsistencies. For example, some predictive modelling studies indicated that the transdiagnostic approach was only able to explain an additional 1% of the variance[109]. Other studies acknowledged that the observed transdiagnostic effects were small in magnitude, but at the same time suggested developing transdiagnostic clinical interventions[131].

In general, neuroscientific studies provided better descriptions of these effects. For example, one of them concluded that the transdiagnostic biotypes identified specific, coherent associations between symptoms, behavior, brain function, and real-world function that cut across DSM-IV defined diagnoses[111]. Other neuroscientific studies demonstrated shared neurobiological mechanisms across current categories of mental disorders[108,112,113,115,117] or both specific and transdiagnostic effects across mental disorders[74,116,129].

Quality assessment

A substantial proportion of studies (40%)[23,28-30,37,40,47,67,69-71,73,75,78,80,82-88,93,96-98,100,104-109,113-118,120,124,126,128,130] did not acknowledge an *a priori* protocol. There were very few studies reporting industry involvement (4%)[52,57,103,110,111]. Transdiagnostic findings were hardly ever externally replicated, with the exception of four studies (4%)[73,85,93,111]. Other methodological weaknesses involved the use of clinical prediction methods (i.e., stepwise selection methods) that produce biased models[109,82], in particular in small databases[131,120,80]. The use of small samples[80] also led to underpowered analyses across diagnostic subgroups[133].

Some studies interpreted overfitted and not externally replicated models to favor transdiagnostic over disorder-specific approaches[76]. Other studies conducted a large number of comparative analyses without controlling for multiple comparisons[106]. One study stated that participants were randomized, but eventually allocated them to a single treatment arm[38]. Another study re-analyzed data from three previously published interventional studies that adopted different designs, without clarifying how the final database was amalgamated[47].

Literature analysis

Mansell's transdiagnostic criteria

Only three studies (3%)[98,100,117] met Mansell's transdiagnostic criteria. The most frequently unmet requirement was the demonstration of the transdiagnostic construct across all conditions investigated by the study.

Type of transdiagnostic approach

The majority of studies (82 out of 111, 74%) (Table 1) endorsed an across-diagnoses approach. Of them, 33 (40%) were conducted within the same diagnostic spectrum (three of which also included a non-clinical sample) and 49 (60%) were across different diagnostic spectra (22 of which also included a non-clinical sample) (Table 1). Only three studies (3%)[111,126,130] endorsed a beyond-diagnoses approach. They were also the most methodologically sophisticated.

For most of these across/beyond-diagnoses studies, the transdiagnostic approach was intertwined in the baseline recruitment of participants with different diagnoses. However, two studies (2%) defined their transdiagnostic approach through the inclusion of different diagnostic outcomes, as opposed to different patient groups at baseline (these studies were termed "transdiagnostic outcomes")[75,77]. Two other studies (2%)[24,51] defined their transdiagnostic approach as the overlap between physical (gastrointestinal, headache) and mental health (anxiety and depression) symptoms (these studies were termed "across physical and mental health diagnoses").

Despite their self-proclaimed transdiagnostic status, the remaining 22 studies (20%) were actually not transdiagnostic at all.

Eight studies (7%)[70,78,82,85,87,92,95,97] did not consider any ICD/DSM diagnostic information as gold standard nor defined any new diagnostic construct. These were usually population-based studies which adopted a continuum rather than a categorical measurement of psychopathology, the results of which were

completely unrelatable to any existing ICD/DSM category. Therefore, these studies were termed as being "a-diagnostic" rather than transdiagnostic.

Five studies (5%)[29,86,88,90,91] confounded symptoms and disorders. These studies explored only DSM or ICD-related symptoms without any clear reference to diagnostic categories of mental disorders, and were therefore defined as "across symptoms".

Nine studies (8%)[50,59-63,96,109,110] were defined as "within the same diagnosis". Six of them investigated comorbid disorders in addition to a single primary disorder: comorbid depression, generalized anxiety disorder and social anxiety disorder in addition to panic disorder[60]; comorbid depression, generalized anxiety disorder and panic disorder in addition to social anxiety disorder[61]; comorbid generalized anxiety disorder, panic disorder and social anxiety disorder in addition to major depressive disorder[62]; comorbid major depressive disorder, social anxiety disorder and panic disorder in addition to generalized anxiety disorder[63]; comorbid panic disorder, social anxiety disorder and generalized anxiety disorder in addition to major depression[50]; and multiple mental disorders in addition to binge eating disorder[59]. Another study investigated comorbid depressive and anxiety symptoms (but not disorders) in patients with post-traumatic stress disorder[110].

Two further studies used the investigated different subtypes (restricting type and binge eating type) of the same disorder (DSM-IV anorexia nervosa)[96] or different clinical states of the same disorder (never depressed, past depression, current depression)[109].

Bibliometric analysis

Figure 3 illustrates the network of specific mental disorders that have been investigated by transdiagnostic research to date. A predominant focus on anxiety and depressive disorders is evident.

DISCUSSION

To the best of our knowledge, this is the most comprehensive review systematically appraising transdiagnostic research in psychiatry. The empirical analysis revealed that the transdiagnostic literature is heterogeneous and intrinsically incoherent. The bibliometric analysis showed that, to date, transdiagnostic research has focused on a limited number of mental disorders. The conceptual analysis leveraged these findings to demonstrate that, at present, transdiagnostic research does not represent a credible paradigm shift that can impact the classification of or clinical care for mental disorders.

This systematic review provides several lines of evidence showing that transdiagnostic approaches in psychiatry are heterogeneous. For example, only three studies out of 111 qualified as being truly transdiagnostic, according to established criteria[21]. This empirical test demonstrates that the transdiagnostic designation is applied in a loose and unstandardized way, encompassing a number of different and often conflicting conceptualizations.

Figure 3 Network map of specific mental disorders analyzed by transdiagnostic research in psychiatry to date. Each node indicates a specific mental disorder, with the node's size reflecting how many different connections with other nodes were present. The thickness of the edges reflects the number of connections between a pair of nodes/mental disorders.

Paradoxically, some of these approaches were intrinsically incoherent and incompatible with a transdiagnostic framework, because they investigated symptoms and not disorders (across-symptoms), a single disorder (within-disorder) or, to the extreme, reported no diagnostic information at all (a-diagnostic).

Furthermore, transdiagnostic studies were often characterized by methodological weaknesses. For example, the exact ICD/DSM types of mental disorders were frequently poorly defined, raising the question of how the researchers could legitimately challenge the boundaries of mental disorders, if these were not even accurately determined. In addition, the boundaries between primary and comorbid disorders in transdiagnostic literature have often been blurred. Arguably, transdiagnostic approaches have been more heterogeneous, incoherent and paid less attention to the problem of comorbidities than the DSM/ICD diagnoses that were criticized for the very same problems.

The other key methodological caveat was that transdiagnostic studies often tested several outcomes, enhancing the likelihood of type I error from data fishing expeditions. This problem was amplified by the use of arbitrary cut-offs to measure symptom severity[134], a general lack of external replication studies, and by overenthusiastic interpretations of the results. In line with these arguments, there were only a few methodologically sound studies which have been able to identify robust mechanistic transdiagnostic constructs that were causally related with the outcome of interest.

Consistent with the above limitations, most transdiagnostic studies (excluding those not properly transdiagnostic, as noted above) limited their analyses to the search for shared features across a certain set of mental disorders (across-diagnoses). However, the bibliometric analysis revealed that these studies remained almost entirely confined within the restricted original area of interest of transdiagnostic research: anxiety and depressive disorders.

No universal transdiagnostic process has been identified, and the extent to which transdiagnostic approaches could pragmatically benefit other mental disorders and diagnostic spectra is undetermined. In fact, only a few transdiagnostic studies have eventually tested new classification systems, beyond the existing gold standard (beyond-diagnoses).

To date, the contribution of transdiagnostic literature to the development and validation of an alternative classification system, which has genuine clinical value – and which is not a "fudge"[135] – has been negligible. Notably, transdiagnostic approaches have not replaced classification systems in any other branches of clinical medicine. On the contrary, continuous (transdiagnostic) and categorical (specific-diagnostic) dimensions frequently co-exist in organic medicine (e.g., vascular surgery)[136], as well as in psychiatry (e.g., the new DSM-5 dimensional approach to personality disorders[137]). In reality, transdiagnostic studies have also produced evidence to support the existence of diagnostic categories[130,138].

It is thus apparent that future extensive research in this field is greatly needed, in particular beyond-diagnoses studies that include several diagnostic spectra. However, a key prerequisite would be to overcome the empirical weaknesses of current transdiagnostic research. To facilitate this outcome, we propose in Table 2 some pragmatic "TRANSD"iagnostic guidelines. We hope these guidelines will improve the consistency and quality of the next generation of transdiagnostic research.

Transdiagnostic research is also affected by some significant conceptual weaknesses. First, it is less innovative than it often proclaims. The fundamental argument for transdiagnostic approaches is that diagnostic categories (mostly anxiety, depressive and eating disorders) are not discrete entities, because there are shared features cutting across them. However, twenty-four years ago, when the DSM-IV was released, an official disclaimer was added to its forefront: "there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders"[139].

It has to be considered that current polythetic (i.e., based on a list of symptoms and signs believed to be characteristic[140]) diagnostic categories originate in prototypical descriptions containing a core structure (gestalt) of the disorder and its polysymptomatic manifestations. Accordingly, the boundaries of mental disorders, as illustrated in Figure 1, are dotted, not solid. Unfortunately, psychiatric knowledge has overlooked these issues and, over the ensuing two decades, the abstract (rather than physical) nature of DSM-IV categories[141] has been reified to the point that they are often seen as real ontological entities, discrete and demarcated from each other by distinct boundaries.

During this process, the symptoms shared by two or several mental disorders tended to be omitted from the diagnostic lists, in order to strengthen the clinical distinctiveness of the categories[140]. Therefore, transdiagnostic research represents more of a rediscovery of what has been forgotten from proto-

Table 2 "TRANSD"iagnostic research recommendations in psychiatry

Transparent definition of the gold standard (ICD, DSM, other), including specific diagnostic types, official codes, primary vs. secondary diagnoses, diagnostic assessment interviews.
Report the primary outcome of the study, the study design and the definition of the transdiagnostic construct in the abstract and main text.
Appraise the conceptual framework/approach of the transdiagnostic approach: across-diagnoses, beyond-diagnoses, other (explain).
Numerate the diagnostic categories, spectra and non-clinical samples in which the transdiagnostic construct is being tested and then validated.
Show the degree of improvement of the transdiagnostic approach against the specific diagnostic approach through specific comparative analyses.
Demonstrate the generalizability of the transdiagnostic construct through external validation studies.

typical descriptions as well as the consequence of the diagnostic reification. In fact, it would make no sense to challenge the diagnostic boundaries without assuming that these do exist on some ontological level.

Second, transdiagnostic approaches are largely based on an epistemological error, which triggers an illusion of continuity[142]. The devaluation[143] and simplification of psychopathological phenomena – introduced by recent versions of the DSM and ICD – to brief, ordinary, non-technical lay language descriptions, has converted complex symptoms and psychic phenomena into phenomenological primitives or homogeneous elementals[140]. For example, there is only one kind of depressive state, one kind of anxiety, one kind of delusion, and it is assumed that all of these states share the same phenomenological structure when they are observed in different mental disorders[140]. Consequently, mental disorders, solely constituted by aggregates of such elementals, lose their characteristic salience, and their clinical boundaries become blurred[140].

An illustrative example is provided by the use of self-report psychometric scales that – not surprisingly – are frequently adopted in transdiagnostic research in order to reduce psychopathology to elementals. Some studies measured the severity of "a specific symptom of depression"[78] in children through self-reported lay statements such as "I am sad once in a while", "I am sad many times" and "I am sad all the time"[78]. The trivialization of the contextual significance of these statements[144] (there are potentially infinite reasons why one could feel sad), is associated with the deprivation of any phenomenological framework (e.g., subjective appraisal of sadness, level of insight, presence of existential despair, perception of time)[145,146]. Such a simplification process transforms these statements into self-contained atomic symptoms[147], which become highly blurred and aspecific, in contrast with the claim of the authors that they are specific symptoms. This point is empirically confirmed by the fact that transdiagnostic literature frequently confounded the measurement of psychometric items in non-clinical samples with clinical symptoms and/or established mental disorders.

Third, the highest interest and biggest clinical contribution of transdiagnostic research has been in the development of emotion-focused cognitive behavioral therapy (CBT) protocols (e.g., the Unified Protocol[58]) for anxiety disorders. A recent meta-analysis indicated that these transdiagnostic treatments lack clinical superiority compared to diagnostic-specific treatments[148].

Although these results and the Unified Protocol are presented as a breakthrough, they are again more like a rediscovery. In fact, psychotherapy was broadly transdiagnostic, driven by a psychoanalytical focus on core emotional issues (termed neurotic conflicts) until 1980, when the DSM-III initiated a gradual splitting of psychopathology into psychiatric categories[149]. This led to an outpouring of CBT diagnosis-specific protocols, which have allowed CBT to balkanize and dominate the psychotherapeutic landscape for over two decades[149]. In this context, some authors have interpreted the Unified Protocol as the end of the CBT-centric dominion and as the resurgence of psychodynamic psychotherapies[149].

This review has some limitations. Because of the intrinsic heterogeneity in the design, methodology and topic covered, we were unable to perform quantitative analyses. However, our main aim was to provide an extensive, detailed snapshot of transdiagnostic research and not to produce summary estimates. Furthermore, there are most probably other studies that have implicitly employed transdiagnostic approaches which have not been included in this review. However, to deconstruct the core characteristics of transdiagnostic research, we selectively focused on those studies that have explicitly acknowledged transdiagnostic approaches as their core distinctive features in their titles.

In conclusion, transdiagnostic research in psychiatry has, to date, been overenthusiastic and undercritical, heterogeneous, intrinsically incoherent and predominantly focused on a limited subset of mental disorders. It is grounded more in rediscoveries than true innovations, and it is demonstrably affected by conceptual biases. Medicine has always worked by a gradual evolutionary evidence-based process and, before rejecting time-tested and progressively refined concepts that are rooted in clinical tradition[5,102], a reliable and valid alternative is needed[150].

To date, transdiagnostic approaches have not delivered the substantial empirical clinical "meat"[135] required for them to represent a credible paradigm shift[5]. The risk of an acritical endorsement of transdiagnostic approaches would be to throw the baby out with the bathwater[151] and be lost in a controversial[102] *mare magnum* of diagnostic uncertainty that may be deleterious for patients and clinicians[5].

Transdiagnostic research has promised (too) much to psychiatry. It is hoped that this review will guide the next generation of transdiagnostic research to complement, refine and improve – less likely to replace[5,136] – the way we currently classify and treat mental disorders.

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Long-term effectiveness of oral second-generation antipsychotics in patients with schizophrenia and related disorders: a systematic review and meta-analysis of direct head-to-head comparisons

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Second-generation antipsychotics (SGAs) are recommended for maintenance treatment in schizophrenia. However, comparative long-term effectiveness among SGAs is unclear. Here we provide a systematic review and meta-analysis of randomized trials lasting ≥6 months comparing SGAs head-to-head in schizophrenia and related disorders. The primary outcome was all-cause discontinuation. Secondary outcomes included efficacy and tolerability, i.e., psychopathology, inefficacy-related and intolerability-related discontinuation, relapse, hospitalization, remission, functioning, quality of life, and adverse events. Pooled risk ratio and standardized mean difference were calculated using random-effects models. Across 59 studies (N=45,787), lasting 47.4±32.1 weeks (range 24-186), no consistent superiority of any SGA emerged across efficacy and tolerability outcomes. Regarding all-cause discontinuation, clozapine, olanzapine and risperidone were significantly (p<0.05) superior to several other SGAs, while quetiapine was inferior to several other SGAs. As to psychopathology, clozapine and olanzapine were superior to several other SGAs, while quetiapine and ziprasidone were inferior to several other SGAs. Data for other efficacy outcomes were sparse. Regarding intolerability-related discontinuation, risperidone was superior and clozapine was inferior to several other SGAs. Concerning weight gain, olanzapine was worse than all other compared non-clozapine SGAs, and risperidone was significantly worse than several other SGAs. As to prolactin increase, risperidone and amisulpride were significantly worse than several other SGAs. Regarding parkinsonism, olanzapine was superior to risperidone, without significant differences pertaining to akathisia. Concerning sedation and somnolence, clozapine and quetiapine were significantly worse than some other SGAs. In summary, different long-term SGA efficacy and tolerability patterns emerged. The long-term risk-benefit profiles of specific SGAs need to be tailored to individual patients to optimize maintenance treatment outcomes.

Key words: Second-generation antipsychotics, maintenance treatment, randomized controlled trials, treatment discontinuation, efficacy, tolerability, clozapine, olanzapine, risperidone

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Schizophrenia is a mental disorder whose course is generally characterized by repeated relapses as well as a worsening of psychopathology and social functioning, thus requiring maintenance treatment[1-3]. Antipsychotics are efficacious for relapse prevention in chronic and first-episode patients[4,5], reducing relapse risk by 2-6-fold versus no antipsychotic treatment[2,4-6].

A previous meta-analysis by our group, comparing second-generation antipsychotics (SGAs) with first-generation antipsychotics (FGAs), found that the former as a class were superior to the latter regarding relapse prevention, all-cause discontinuation and other relapse-related outcomes[3].

Despite the importance of long-term treatment in schizophrenia, in which the magnitude of benefits and risks of medications may be different from acute phase treatment, no comprehensive meta-analysis of the comparative long-term effectiveness, efficacy and safety among oral SGAs currently exists[7].

Although one meta-analysis targeted maintenance trials that compared antipsychotics with placebo[2], indirect comparisons using placebo as the common comparator are not conclusive[8]. Further, a multiple treatment meta-analysis, which includes indirect comparisons, is not necessarily ideal, especially when the number of trials comparing antipsychotics directly is limited and when homogeneity of these trials cannot be assured[9].

Knowledge about the comparative effectiveness, efficacy and tolerability of SGAs in the long-term treatment of schizophrenia is important[7]. Specifically, differences in side effect risk[9-11], some of which may increase with time, need to be weighed against potential differences in long-term effectiveness and efficacy.

Here we report the results of the first comprehensive meta-analysis of head-to-head randomized controlled trials comparing two or more SGAs in the long-term treatment of schizophrenia, aiming to assess the comparative effectiveness, efficacy and safety of these medications.

METHODS

The meta-analysis was performed following PRISMA guidelines[12].

Search and inclusion criteria

We conducted an electronic search without language restrictions using MEDLINE/PubMed, the Cochrane library, ISI Web of Science, PsycINFO, CINAHL and the US National Institutes of Health clinical trials registry (http://www.clinicaltrials.gov). The following search terms were used: antipsychotic(s); neuroleptic(s); individual names of SGAs; schizophrenia; random, randomly, randomized; and maintenance, relapse, discontinuation or long-term. The last search was done on October 29,

2018. The electronic search was supplemented by a hand search of reference lists of relevant studies and reviews. Authors and companies were contacted to provide missing information and unpublished data.

We included randomized, head-to-head comparisons of oral SGAs in adults with schizophrenia or schizoaffective disorder which reported on treatment discontinuation, whether randomization occurred during the acute or maintenance phase. As we aimed to focus on the comparative long-term effectiveness of SGAs, we only included head-to-head studies lasting ≥6 months.

We excluded studies with >20% of non-schizophrenia/schizoaffective disorder patients. As long-acting injectable formulation enhances the adherence and therefore has a significant impact on long-term outcome[13,14], we excluded studies on long-acting antipsychotics.

The search, selection of the literature, and data extraction were conducted independently by ≥2 reviewers (KH, MN, TK, CC). Disagreements were resolved by consensus.

Outcomes

The primary outcome was all-cause discontinuation at study endpoint.

Secondary outcomes included: a) psychopathology score change, measured by the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS) or the Clinical Global Impression - Severity (CGI-S) score (mixed models or last-observation-carried-forward was prioritized over observed cases analysis); b) inefficacy-related discontinuation (as reported by the original study authors); c) intolerability-related discontinuation (as reported by the original study authors); d) relapse (as reported by the original study authors); e) hospitalization; f) remission (as reported by the original study authors); g) functioning score; h) quality of life (QOL); and i) adverse events.

Adverse events included: weight gain (as change from baseline or proportion of patients with clinically significant increase); prolactin increase (as change from baseline or proportion of patients with hyperprolactinemia); neuromotor adverse effects, including parkinsonism assessed with the Simpson-Angus Rating Scale or use of anticholinergics, akathisia and dyskinesia; and sedation and/or somnolence.

Data analysis

SGAs were compared individually for each outcome. We applied a "once-randomized-analyzed" intent-to-treat (ITT) endpoint analysis. In studies that followed patients even after they were switched off the originally allocated medication during the study period, we analyzed the primary outcome based only on the first medication but, for secondary outcomes, we extracted and analyzed the data as reported in the ITT sample.

Pooled risk ratio (RR) and standardized mean difference (SMD) with 95% confidence intervals (CIs) were calculated using random-effects models[15]. RR values <1 indicate superiority of the first SGA for negative outcomes (such as all-cause discontinuation, relapse, inefficacy-related and intolerability-related discontinuation), while RR values >1 indicate superiority for the only positive outcome, remission. For simplicity we adjusted effect sizes, so that SMDs <0 indicate superiority of the first SGA, independent of whether a lower value (e.g., psychopathology) or higher value (e.g., functioning, QOL) is a positive outcome.

Number-needed-to-treat (NNT) was calculated when categorical outcome differences were significant. Heterogeneity was only inspected when ≥2 studies were analyzed, using the chi-square test ($p<0.1$ indicating significant heterogeneity)[16] and the I^2 statistic ($I^2 \geq 50\%$ indicating significant heterogeneity)[17]. For study quality assessment, we used the Jadad scale[18], that provides a sum score for sensitivity analyses.

In addition, *a priori*-defined subgroup analyses of the primary outcome were conducted (where ≥2 studies existed), seeking to identify potential moderators, methodological biases, and whether findings extended to clinically relevant subpopulations or treatment groups. Subgroup analyses included: a) randomization time point (acute vs. maintenance phase); b) sponsorship (medication-specific sponsor vs. academia); c) study quality (high vs. low Jadad score)[18]; d) concealment (open or single-blinded vs. double-blinded); e) location (international/USA/Europe/Asia); f) dosing (fixed vs. flexible), and g) first episode vs. chronically ill.

Comprehensive Meta-Analysis, version 3 (Biostat, NJ, USA) was used for all two-tailed analyses, with alpha=0.05, without adjustments for multiple comparisons. Publication bias was assessed with the funnel plot, Egger's regression test[19] and the "trim and fill" method[20] for the primary outcome, whenever ≥3 studies were analyzed.

RESULTS

Search and study characteristics

A total of 8,611 references were identified (Figure 1). After removing 152 duplicates, we excluded 7,823 of the remaining 8,459 references based on title/abstract inspection. Of 113 references subjected to full-text inspection, 54 articles were dropped because of: inappropriate participants (N=17), review/editorial (N=11), no usable data (N=10), inappropriate medication (N=6), short-term study (N=4), no/inadequate randomization (N=3), and meeting abstracts of already included studies (N=3).

Altogether, we included 63 reports[21-83] (59 randomized studies) with 45,787 participants (median: 255 participants/study, range: from 12 to 18,154) (Table 1). The mean age of the population was 37.6±7.0 years; 62.1±13.3% were male and 61.1±28.8% were white. The mean study duration was 47.4±32.1 weeks (range: 24-186).

Forty-six studies included multiple-episode patients, eight included exclusively first-episode patients, four included exclusively treatment-resistant patients (all clozapine studies),

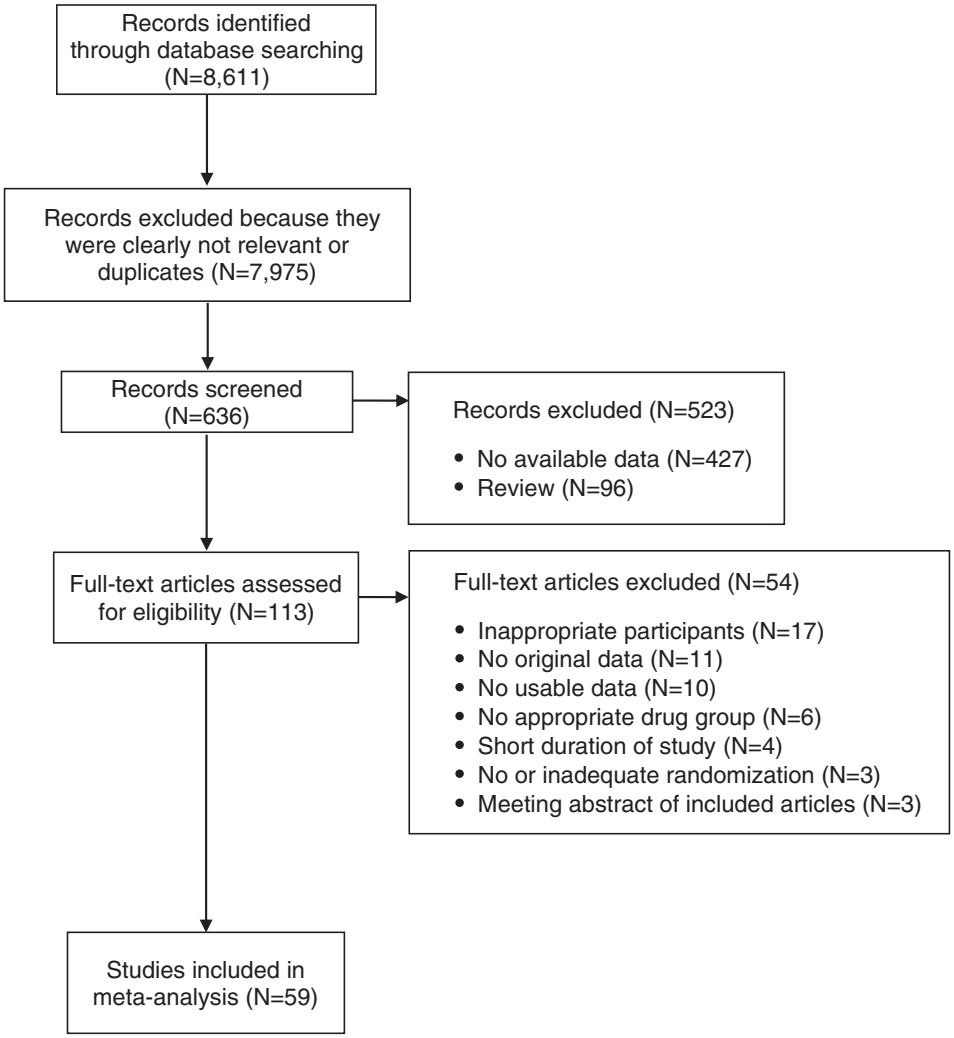


Figure 1 PRISMA flow chart

and one did not report the number of episodes of included patients[79]. Thirty-four studies were double-blind, 20 were open-label, and five had masked raters. Forty studies were sponsored by pharmaceutical companies, 18 were publicly funded, and funding was uncertain in one study[77].

The number of studies with each individual SGA were: 43 for olanzapine, 27 for risperidone, 15 for quetiapine, 12 for ziprasidone, 12 for aripiprazole, eight for clozapine, four for amisulpride, four for asenapine, two for lurasidone, two for paliperidone, one for blonanserin, one for cariprazine, and one for sertindole.

Thirty-nine studies (66.1%) randomized patients in the acute phase, eighteen (30.5%) in the maintenance phase, while the randomization time point was uncertain for two studies (3.4%)[60,64]. Two studies[33,76] utilized an enriched design, in that patients stabilized on drug A were randomized to continued treatment or switch to drug B. Two studies[70,75] had a "naturalistic" follow-up design, in that switches off the originally assigned drugs were allowed.

Eleven studies reported on relapse, and six on remission. The definition of relapse varied, with only two studies using the same criteria[28,47]. Three[8,31,37] out of six studies reporting on remission used Andreasen et al's criteria[84].

Primary outcome measure: all-cause discontinuation

Across 59 studies, the pooled effect sizes of individual SGA pairs concerning all-cause discontinuation are shown in Figure 2.

Clozapine had a significantly lower all-cause discontinuation as compared with quetiapine (one study, N=64, RR=0.59, 95% CI: 0.42-0.83, p=0.002) and risperidone (four studies, N=216, RR=0.74, 95% CI: 0.57-0.95, p=0.020, I^2=5.1%). Olanzapine had a significantly lower all-cause discontinuation as compared with paliperidone (one study, N=459, RR=0.64, 95% CI: 0.46-0.90, p=0.010), quetiapine (eight studies, N=1,942, RR=0.79, 95% CI: 0.71-0.89, p<0.001, I^2=55.8%), risperidone (16 studies, N=3,131, RR=0.88, 95% CI: 0.83-0.93, p<0.001, I^2=0.0%), and ziprasidone (eight studies, N=20,225, RR=0.82, 95% CI: 0.77-0.87, p<0.001, I^2=37.0%). Risperidone had a significantly lower all-cause dis-

Table 1 Characteristics of included studies

Study	Country	Blinding status	N. patients	Randomization time point	Duration (weeks)	First episode/ chronically ill	Mean age	% male	Comparison	Dose (mean, mg/day)	Jadad score
Addington et al[21]	International	DB	139	Maintenance	44	Chronically ill	34.6	65.5	RIS vs. ZIP	8; 114	3
Alvarez et al[22]	Spain	DB	50	Acute	24	Chronically ill	38.4	70.0	OLZ vs. ZIP	15; 107.4	3
Alvarez et al[23]; Ciudad et al[24]	Spain	OL	235	Maintenance	48	Chronically ill	36.5	72.3	OLZ vs. RIS	12.2; 4.9	2
Breier et al[25]	International	DB	548	Acute	28	Chronically ill	39.2	64.2	OLZ vs. ZIP	15.27; 115.96	3
Chan et al[26]	Taiwan	RB	60	Acute	24	Chronically ill	45.4	35.0	OLZ vs. RIS	4.1; 12.6	3
Chrzanowski et al[27]	International	OL	214	Acute	52	Chronically ill	41.5	54.0	APZ vs. OLZ	22; 14.2	2
Citrome et al[28]	International	DB	629	Maintenance	52	Chronically ill	41.7	69.0	LUR vs. RIS	84.7; 4.3	4
Crespo-Facorro et al[29]	Spain	OL	202	Acute	52	First episode	32.0	53.5	APZ vs. QTP vs. ZIP	11.6; 311.4; 61.0	3
Crespo-Facorro et al[30]	Spain	OL	174	Acute	156	First episode	27.3	62.1	OLZ vs. RIS	12.9; 3.4	1
de Arce Cordón et al[31]; Gaebel et al[32]	International	OL	711	Maintenance	104	Chronically ill	41.6	57.8	APZ vs. QTP	15.1; 413.4	2
Deberdt et al[33]	USA	DB	133	Maintenance (enriched design)	26	Chronically ill	44.0	NR	OLZ vs. QTP	16.9; 439.7	3
Durgam et al[34]	International	DB	120	Acute	26	Chronically ill	39.6	59.2	ASN vs. OLZ	Fixed dose: 5 or 10; 15	4
Fleischhacker et al[35]	International	DB	488	Acute	46	Chronically ill	36.6	56.8	APZ vs. OLZ	23.0; 15.4	4
Kahn et al[36]	International	OL	498	Acute	52	First episode	26.0	60.0	AMI vs. OLZ vs. QTP vs. ZIP	450.8; 12.6; 498.6; 107.2	3
Kane et al[37]	International	DB	566	Acute	28	Chronically ill	37.8	67.8	APZ vs. OLZ	19.3; 16.7	3
Keefe et al[38]	International	DB	414	Acute	52	Chronically ill	39.1	71.3	OLZ vs. RIS	12.3; 5.2	3
Kern et al[39]	USA	OL	255	Acute	2 6	Chronically ill	40.0	64.5	APZ vs. OLZ	NR	2
Kinon et al[40]	USA	DB	346	Acute	24	Chronically ill	41.1	65.9	OLZ vs. QTP	15.6; 455.8	4
Kinon et al[41]	USA	DB	394	Acute	24	Chronically ill	41.6	62.9	OLZ vs. ZIP	Fixed dose:10 or 15 or 20;80 or 120 or 160	3
Kishi et al[42]	Japan	RB	44	Acute	24	Chronically ill	39.5	40.9	APZ vs. BLO	11.5; 10.3	4
Kumar et al[43]	India	DB	71	Maintenance	48	Chronically ill	40.7	50.7	OLZ vs. RIS	14.4; 5.8	3
Lecrubier et al[44]	France	DB	244	Maintenance	26	Chronically ill	37.4	68.6	AMI vs. OLZ	Fixed dose; 150; 5 or 20	3

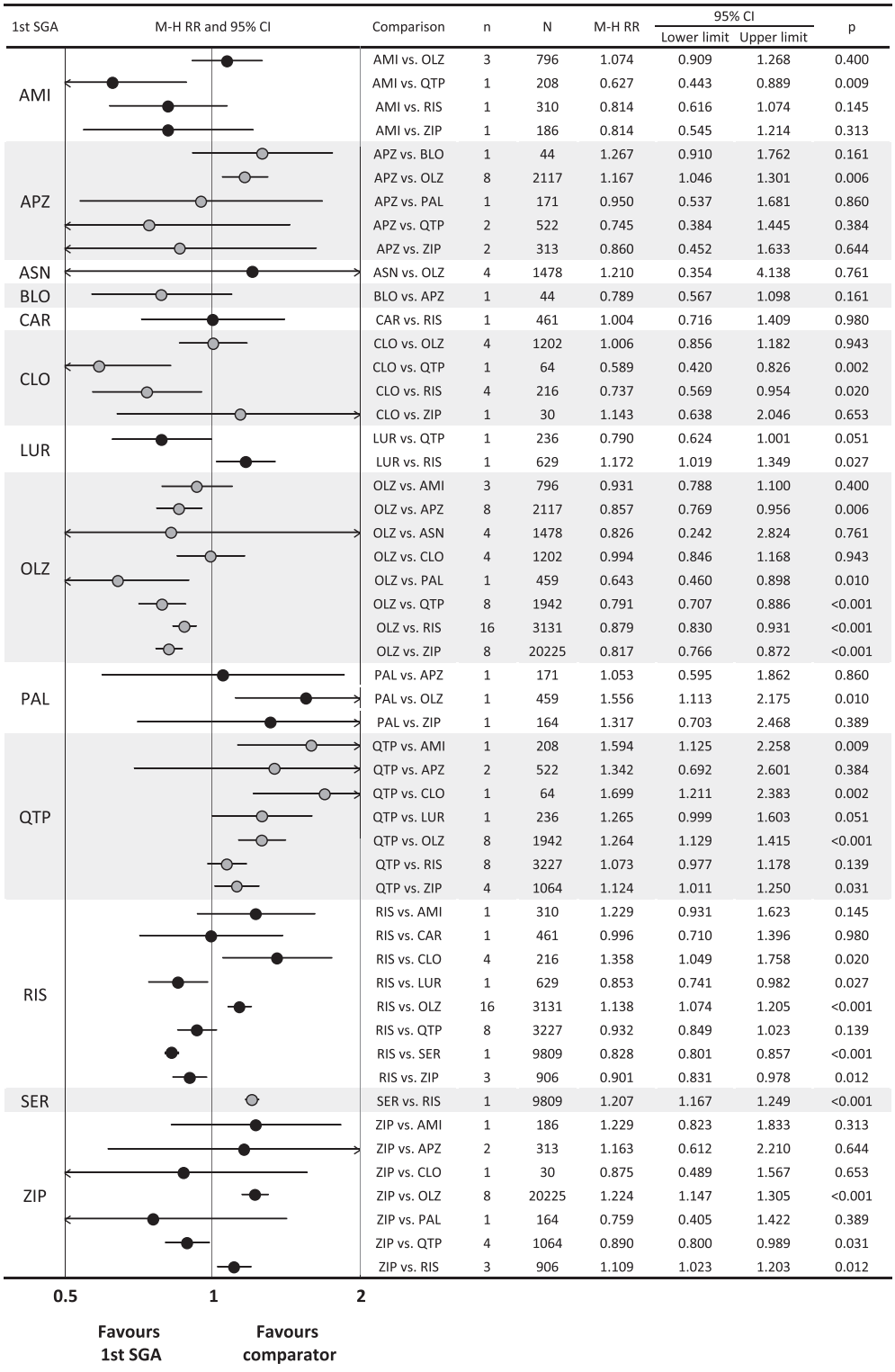
Table 1 Characteristics of included studies (*continued*)

Study	Country	Blinding status	N. patients	Randomization time point	Duration (weeks)	First episode/ chronically ill	Mean age	% male	Comparison	Dose (mean, mg/day)	Jadad score
Lieberman et al[45]	USA	DB	1,460	Acute	78	Chronically ill	40.6	72.3	OLZ vs. QTP vs. RIS vs. ZIP	20.1; 543.4; 3.9;112.8	3
Liu et al[46]	China	OL	80	Acute	52	First episode	29.5	0.00	QTP vs. RIS	420; 3.4	3
Loebel et al[47]; NCT00789698[48]	International	DB	327	Maintenance	52	Chronically ill	37.6	66.8	LUR vs. QTP	NR	4
McEvoy et al[49]	USA	OL	99	Acute	26	Chronically ill	39.7	81.0	CLO vs. OLZ vs. QTPvs. RIS	332.1; 23.4; 642.9;4.8	2
McEvoy et al[50]	USA	DB	400	Acute	52	First episode	24.5	73.0	OLZ vs. QTP vs. RIS	11.7; 506; 2.4	3
McQuade et al[51]	International	DB	317	Acute	26	Chronically ill	38.4	72.0	APZ vs. OLZ	25.1; 16.5	3
Meltzer et al[52]	International	RB	980	Acute	104	Chronically ill	37.1	61.4	CLO vs. OLZ	274.2; 16.6	2
Meltzer et al[53]	USA	DB	40	Acute	26	Chronically ill	36.8	67.5	CLO vs. OLZ	564; 33.6	4
Mortimer et al[54]	International	DB	377	Acute	24	Chronically ill	37.8	65.0	AMI vs. OLZ	504; 13	5
Naber et al[55]	Germany	DB	114	Acute	26	Chronically ill	34.0	61.0	CLO vs. OLZ	209; 16.2	3
Naber et al[56]; NCT00600756[57]	International	OL	798	Acute	52	Chronically ill	39.7	58.2	QTP vs. RIS	NR	3
Németh et al[58]	International	DB	461	Maintenance	26	Chronically ill	40.5	57.4	CAR vs. RIS	Fixed dose: 3 or 4 or 5 or 6; 3 or 4 or 6	5
Noordsy et al[59]	USA	DB	107	Maintenance	24	Chronically ill	42.0	82.2	OLZ vs. RIS	Range: 2.5-30; 1-10	1
Parabiaghi et al[60]	Italy	OL	300	NR	52	Chronically ill	42.7	58.0	APZ vs. OLZ	19.7; 13.7	3
Purdon et al[61]	Canada	DB	65	Maintenance	54	Chronically ill	28.9	70.6	OLZ vs. RIS	11.00; 6.00	4
Ritchie et al[62]	Australia	OL	66	Acute	186	Chronically ill	69.5	28.8	OLZ vs. RIS	NR	2
Sanz-Fuentenebro et al[63]	Spain	OL	30	Acute	52	First episode	24.5	70.0	CLO vs. RIS	220.45; 5.43	2
Schnell et al[64]	Germany	DB	30	NR	52	Chronically ill	29.0	86.7	CLO vs. ZIP	225; 200	3
Schoemaker et al[65]	International	DB	440	Maintenance	96	Chronically ill	36.9	55.5	ASN vs. OLZ	13.4; 13.4	3
Schooler et al[66]	USA	DB	107	Acute	29	Chronically ill	41.9	79.4	CLO vs. RIS	456.7; 6.8	4
Sechter et al[67]	International	DB	310	Acute	26	Chronically ill	38.4	55.0	AMI vs. RIS	683; 6.92	3
Schreiner et al[68]	International	OL	459	Acute	26	Chronically ill	38.2	58.0	OLZ vs. PAL	11.6; 6.9	3
Simpson et al[69]	USA	DB	126	Maintenance	26	Chronically ill	NR	NR	OLZ vs. ZIP	12.6; 135.2	2

Table 1 Characteristics of included studies (*continued*)

Study	Country	Blinding status	N. patients	Randomization time point	Duration (weeks)	First episode/ chronically ill	Mean age	% male	Comparison	Dose (mean, mg/day)	Jadad score
Strom et al[70]	International	OL	18,154	Acute	52	Chronically ill	41.1	55.0	OLZ vs. ZIP	NR	2
Stroup et al[71]	USA	DB	444	Acute	26	Chronically ill	40.8	69.0	OLZ vs. QTP vs. RIS vs. ZIP	20.5; 565.2; 4.1; 115.9	3
Stroup et al[72]	USA	DB	115	Acute	78	Chronically ill	40.8	77.0	OLZ vs. QTP vs. RIS	20.7; 586.1; 3.7	3
Thomas et al[73]	International	OL	9,809	Acute	Mean: 564.0; 489.6 days	Chronically ill	38.3	55.3	RIS vs. SER	Range: 2-8; 12-20	3
Tran et al[74]	International	DB	339	Acute	28	Chronically ill	36.2	64.9	OLZ vs. RIS	17.2; 7.2	3
Tunis et al[75]	USA	OL	450	Acute	52	Chronically ill	43.0	63.0	OLZ vs. RIS	13.49; 4.95	2
Wani et al[76]	India	OL	62	Maintenance (enriched design)	24	Chronically ill	29.8	62.9	APZ vs. OLZ	NR	1
Zhang et al[77]	China	OL	254	Acute	52	First episode	26.4	61.0	APZ vs. PAL vs. ZIP	NR	2
NCT00145496[78]	International	DB	468	Maintenance	26	Chronically ill	42.9	73.9	ASN vs. OLZ	NR	3
NCT00206102[79]	USA	OL	1,098	Maintenance	104	NR	NR	58.8	QTP vs. RIS	Range: 200-800; 2-8	3
NCT00212836[80]	International	DB	481	Maintenance	26	Chronically ill	40.5	68.2	ASN vs. OLZ	NR	2
NCT00236379[81]	International	DB	59	Maintenance	24	Chronically ill	39.7	NR	OLZ vs. RIS	Range: 5-20; 2-6	3
NCT00573287[82]	USA	RB	14	Acute	24	First episode	22.4	57.1	CLO vs. RIS	Range: 12.5-100; 0.5-5.0	1
NCT00802100[83]	USA	RB	12	Acute	28	Chronically ill	29.0	61.9	APZ vs. OLZ	NR	2

AMI – amisulpride, APZ – aripiprazole, ASN – asenapine, BLO – blonanserin, CAR – cariprazine, CLO – clozapine, LUR – lurasidone, OLZ – olanzapine, PAL – paliperidone, QTP – quetiapine, RIS – risperidone, SER – sertindole, ZIP – ziprasidone, DB – double-blind, OL – open label, RB – rater-blinded, NR – not reported



1st SGA	Comparison	n	N	M-H RR	95% CI		p
					Lower limit	Upper limit	
AMI	AMI vs. OLZ	3	796	1.074	0.909	1.268	0.400
	AMI vs. QTP	1	208	0.627	0.443	0.889	0.009
	AMI vs. RIS	1	310	0.814	0.616	1.074	0.145
	AMI vs. ZIP	1	186	0.814	0.545	1.214	0.313
APZ	APZ vs. BLO	1	44	1.267	0.910	1.762	0.161
	APZ vs. OLZ	8	2117	1.167	1.046	1.301	0.006
	APZ vs. PAL	1	171	0.950	0.537	1.681	0.860
	APZ vs. QTP	2	522	0.745	0.384	1.445	0.384
	APZ vs. ZIP	2	313	0.860	0.452	1.633	0.644
ASN	ASN vs. OLZ	4	1478	1.210	0.354	4.138	0.761
BLO	BLO vs. APZ	1	44	0.789	0.567	1.098	0.161
CAR	CAR vs. RIS	1	461	1.004	0.716	1.409	0.980
CLO	CLO vs. OLZ	4	1202	1.006	0.856	1.182	0.943
	CLO vs. QTP	1	64	0.589	0.420	0.826	0.002
	CLO vs. RIS	4	216	0.737	0.569	0.954	0.020
	CLO vs. ZIP	1	30	1.143	0.638	2.046	0.653
LUR	LUR vs. QTP	1	236	0.790	0.624	1.001	0.051
	LUR vs. RIS	1	629	1.172	1.019	1.349	0.027
OLZ	OLZ vs. AMI	3	796	0.931	0.788	1.100	0.400
	OLZ vs. APZ	8	2117	0.857	0.769	0.956	0.006
	OLZ vs. ASN	4	1478	0.826	0.242	2.824	0.761
	OLZ vs. CLO	4	1202	0.994	0.846	1.168	0.943
	OLZ vs. PAL	1	459	0.643	0.460	0.898	0.010
	OLZ vs. QTP	8	1942	0.791	0.707	0.886	<0.001
	OLZ vs. RIS	16	3131	0.879	0.830	0.931	<0.001
	OLZ vs. ZIP	8	20225	0.817	0.766	0.872	<0.001
PAL	PAL vs. APZ	1	171	1.053	0.595	1.862	0.860
	PAL vs. OLZ	1	459	1.556	1.113	2.175	0.010
	PAL vs. ZIP	1	164	1.317	0.703	2.468	0.389
QTP	QTP vs. AMI	1	208	1.594	1.125	2.258	0.009
	QTP vs. APZ	2	522	1.342	0.692	2.601	0.384
	QTP vs. CLO	1	64	1.699	1.211	2.383	0.002
	QTP vs. LUR	1	236	1.265	0.999	1.603	0.051
	QTP vs. OLZ	8	1942	1.264	1.129	1.415	<0.001
	QTP vs. RIS	8	3227	1.073	0.977	1.178	0.139
	QTP vs. ZIP	4	1064	1.124	1.011	1.250	0.031
RIS	RIS vs. AMI	1	310	1.229	0.931	1.623	0.145
	RIS vs. CAR	1	461	0.996	0.710	1.396	0.980
	RIS vs. CLO	4	216	1.358	1.049	1.758	0.020
	RIS vs. LUR	1	629	0.853	0.741	0.982	0.027
	RIS vs. OLZ	16	3131	1.138	1.074	1.205	<0.001
	RIS vs. QTP	8	3227	0.932	0.849	1.023	0.139
	RIS vs. SER	1	9809	0.828	0.801	0.857	<0.001
	RIS vs. ZIP	3	906	0.901	0.831	0.978	0.012
SER	SER vs. RIS	1	9809	1.207	1.167	1.249	<0.001
ZIP	ZIP vs. AMI	1	186	1.229	0.823	1.833	0.313
	ZIP vs. APZ	2	313	1.163	0.612	2.210	0.644
	ZIP vs. CLO	1	30	0.875	0.489	1.567	0.653
	ZIP vs. OLZ	8	20225	1.224	1.147	1.305	<0.001
	ZIP vs. PAL	1	164	0.759	0.405	1.422	0.389
	ZIP vs. QTP	4	1064	0.890	0.800	0.989	0.031
	ZIP vs. RIS	3	906	1.109	1.023	1.203	0.012

Figure 2 Results of comparisons of all-cause discontinuation in meta-analysis of second-generation antipsychotics (SGAs). The first drug is the one written on the left side of the graph, and the comparator is written in the row of comparison. AMI – amisulpride, APZ – aripiprazole, ASN – asenapine, BLO – blonanserin, CAR – cariprazine, CLO – clozapine, LUR – lurasidone, OLZ – olanzapine, PAL – paliperidone, QTP – quetiapine, RIS – risperidone, SER – sertindole, ZIP – ziprasidone, M-H RR – Mantel-Haenszel risk ratio.

continuation as compared with sertindole (one study, N=9,809, RR=0.83, 95% CI: 0.80-0.86, p<0.001) and ziprasidone (three studies, N=906, RR=0.90, 95% CI: 0.83-0.98, p=0.012, I^2=0.0%).

Other significant differences included the following: significantly lower all-cause discontinuation for amisulpride vs. quetiapine (one study, N=208, RR=0.63, 95% CI: 0.44-0.89, p=0.009); significantly higher all-cause discontinuation for aripiprazole vs. olanzapine (eight studies, N=2,117, RR=1.17, 95% CI: 1.05-1.30, p=0.006, I^2=28.8%); significantly higher all-cause discontinuation for lurasidone vs. risperidone (one study, N=629, RR=1.17, 95% CI: 1.02-1.35, p=0.027); and significantly higher all-cause discontinuation for quetiapine vs. ziprasidone (four studies, N=1,064, RR=1.12, 95% CI: 1.01-1.25, p=0.031, I^2=47.0%).

Secondary outcomes

Across 23 SGA comparisons concerning psychopathology, based on 32 studies, the following nine significant differences emerged: aripiprazole was superior to quetiapine and ziprasidone; clozapine was superior to quetiapine and risperidone; lurasidone was superior to quetiapine; olanzapine was superior to paliperidone and risperidone; and paliperidone was superior to aripiprazole and ziprasidone (Figure 3).

Across 26 comparisons concerning intolerability-related discontinuation, based on 50 studies, the following significant differences emerged: quetiapine was superior to amisulpride; risperidone was superior to clozapine, quetiapine and sertindole; and ziprasidone was superior to clozapine (Figure 4).

Across 20 comparisons concerning inefficacy-related discontinuation, based on 47 studies, the following significant differences emerged: aripiprazole was superior to quetiapine; clozapine was superior to risperidone; lurasidone was superior to quetiapine; and olanzapine was superior to aripiprazole, quetiapine and ziprasidone (Figure 5).

Across 11 comparisons concerning relapse, only one significant difference emerged: the superiority of olanzapine over risperidone. Across 13 comparisons concerning hospitalization, clozapine was superior to olanzapine, and lurasidone and risperidone were superior to quetiapine. Across six comparisons concerning remission, lurasidone was superior to quetiapine, and quetiapine was superior to risperidone. Across 12 comparisons concerning functioning, aripiprazole was superior to quetiapine, cariprazine was superior to risperidone, and clozapine was superior to olanzapine. Across 11 comparisons concerning QOL, there were no significant SGA-pair differences.

Twenty-five comparisons based on 46 studies were meta-analyzed for weight gain. Amisulpride, aripiprazole, quetiapine, risperidone, paliperidone and ziprasidone were superior to olanzapine; amisulpride, cariprazine, lurasidone and ziprasidone were superior to risperidone; paliperidone was superior to aripiprazole; and ziprasidone was superior to paliperidone and quetiapine (Table 2).

Prolactin increase was meta-analyzed in 16 comparisons based on 21 studies. Clozapine, lurasidone, olanzapine, quetiapine and ziprasidone were superior to risperidone; aripiprazole and quetiapine were superior to olanzapine; olanzapine, quetiapine and ziprasidone were superior to amisulpride (Table 2).

Parkinsonism was meta-analyzed in 20 comparisons based on 28 studies: olanzapine was superior to risperidone. Dyskinesia was meta-analyzed in 11 comparisons based on 13 studies: ziprasidone was superior to quetiapine. Akathisia was meta-analyzed in 11 comparisons based on 9 studies: no significant differences emerged. Sedation and/or somnolence were meta-analyzed in 17 comparisons based on 27 studies: olanzapine and paliperidone were superior to clozapine, and risperidone was superior to quetiapine.

Subgroup analyses for primary outcome

In subgroup analyses, the significance of the primary results was altered in 49/267 (18.4%) analyses, but most subgroups were very small both in number of studies and patients. Comparative effectiveness patterns were mostly consistent in high-quality studies and double-blind trials.

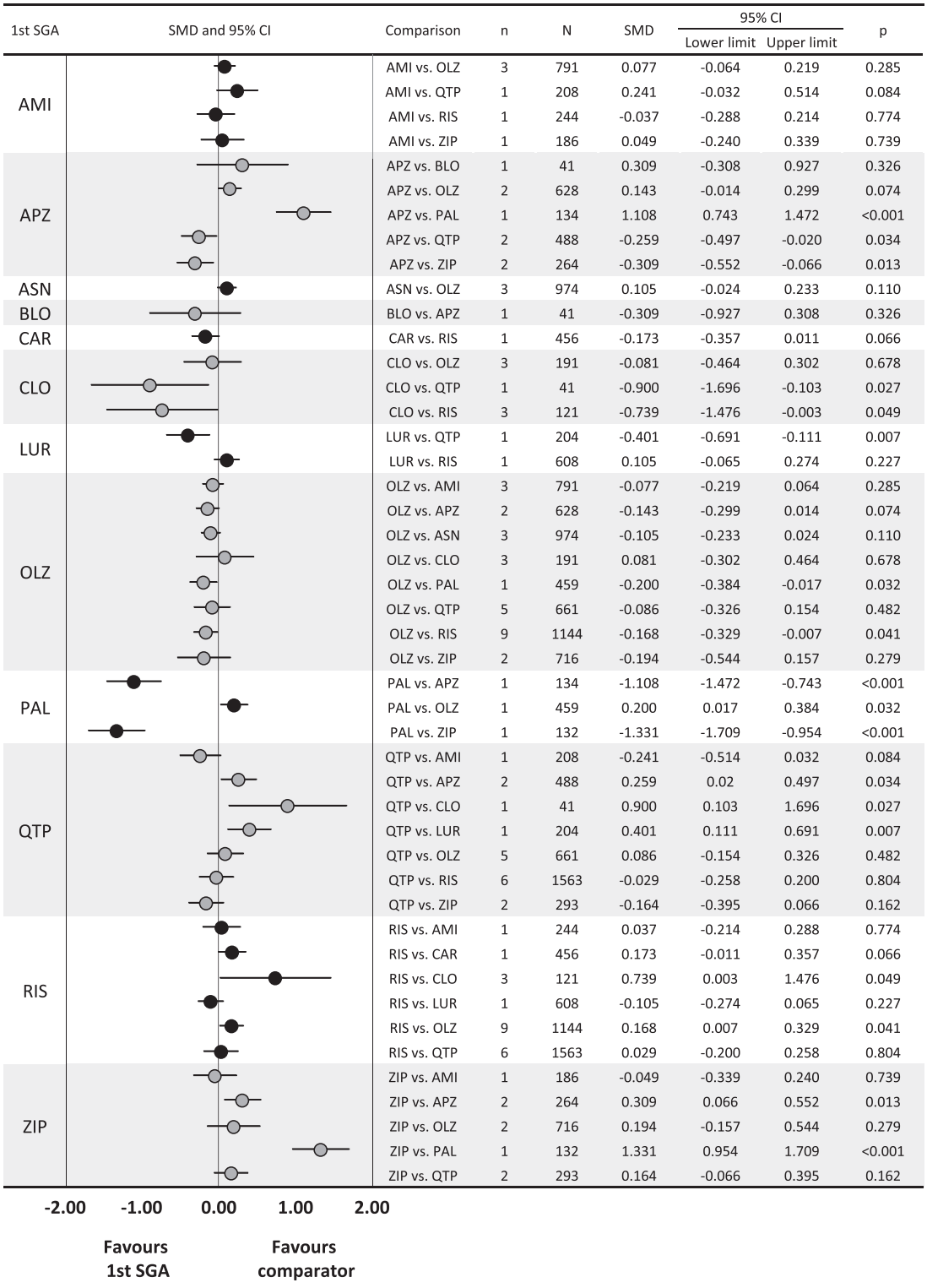
Regarding industry sponsorship, results showing a specific drug's inferiority were neutralized when three of 43 medication-specific manufacturer-sponsored studies were included. In contrast, one outcome showing superiority of olanzapine was neutralized when one manufacturer-funded study was included.

Regarding blinding, some results changed when we restricted the analyses to open label or blinded studies. Restricting the analyses to only blinded studies, 5/39 results that showed statistical significance became non-significant. Restricting the analyses to only open label studies, 1/39 non-significant results became statistically significant.

None of the other potential effect-moderators addressed in subgroup analyses revealed a clear pattern of effect. There were no subgroup analyses in which the direction of the results was reversed.

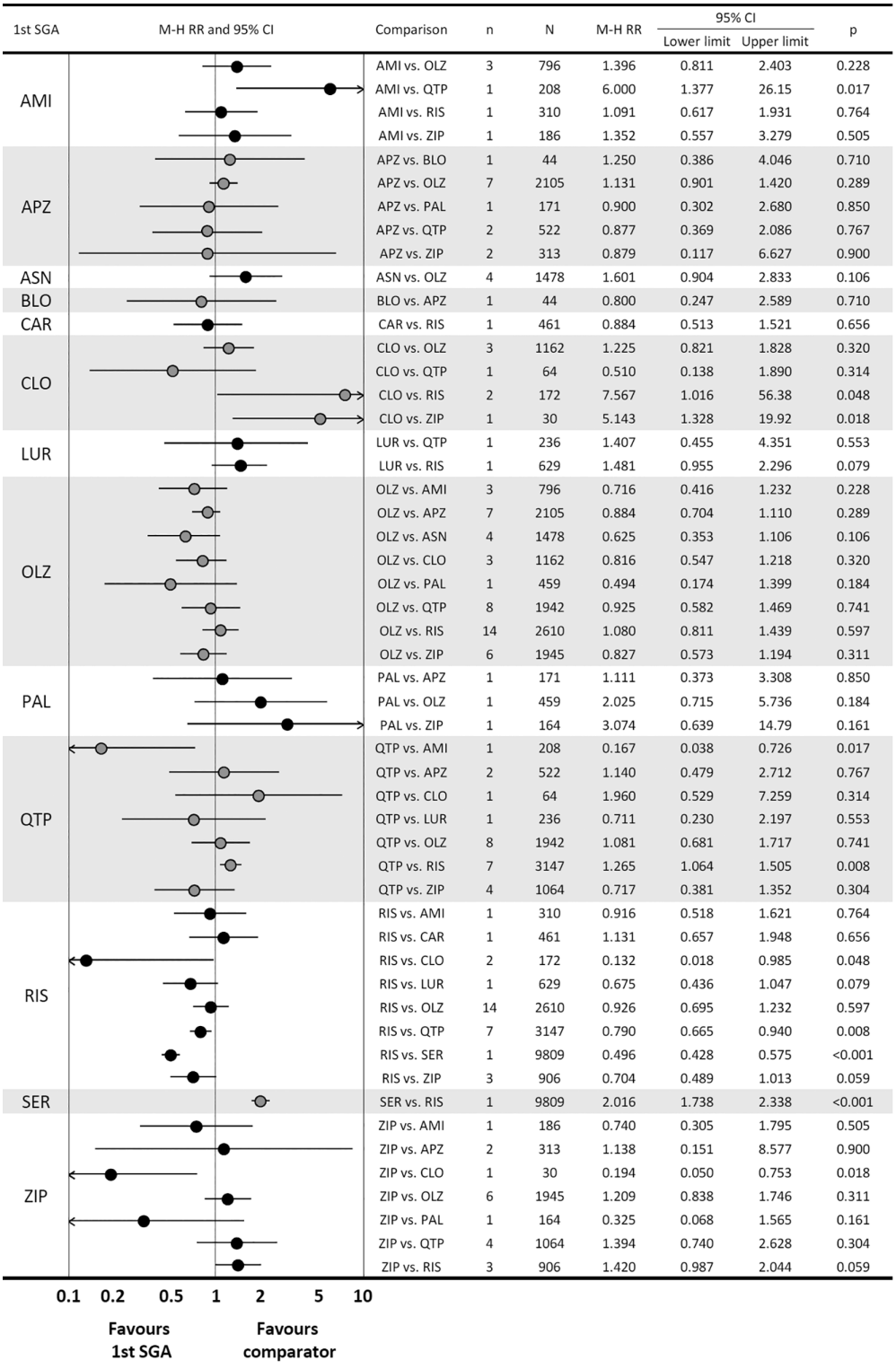
Publication bias

Publication bias for all-cause discontinuation was assessed by funnel plot. In nine of eleven comparisons with ≥3 studies, the funnel plot was asymmetrical. Subsequently, we applied the trim-and-fill method to adjust for potential publication bias, and found that the effect sizes were similar after adjustment, and that the significance for RRs did not change, except for two comparisons. Quetiapine was not different in observed values but became inferior to risperidone in adjusted values (original RR=1.07, 95% CI: 0.98-1.18; adjusted RR=1.11, 95% CI: 1.00-1.24). Quetiapine was significantly inferior in observed values, but became not different from ziprasidone in adjusted values (original RR=1.12, 95% CI: 1.01-1.25; adjusted RR=1.08, 95% CI: 0.98-1.19).



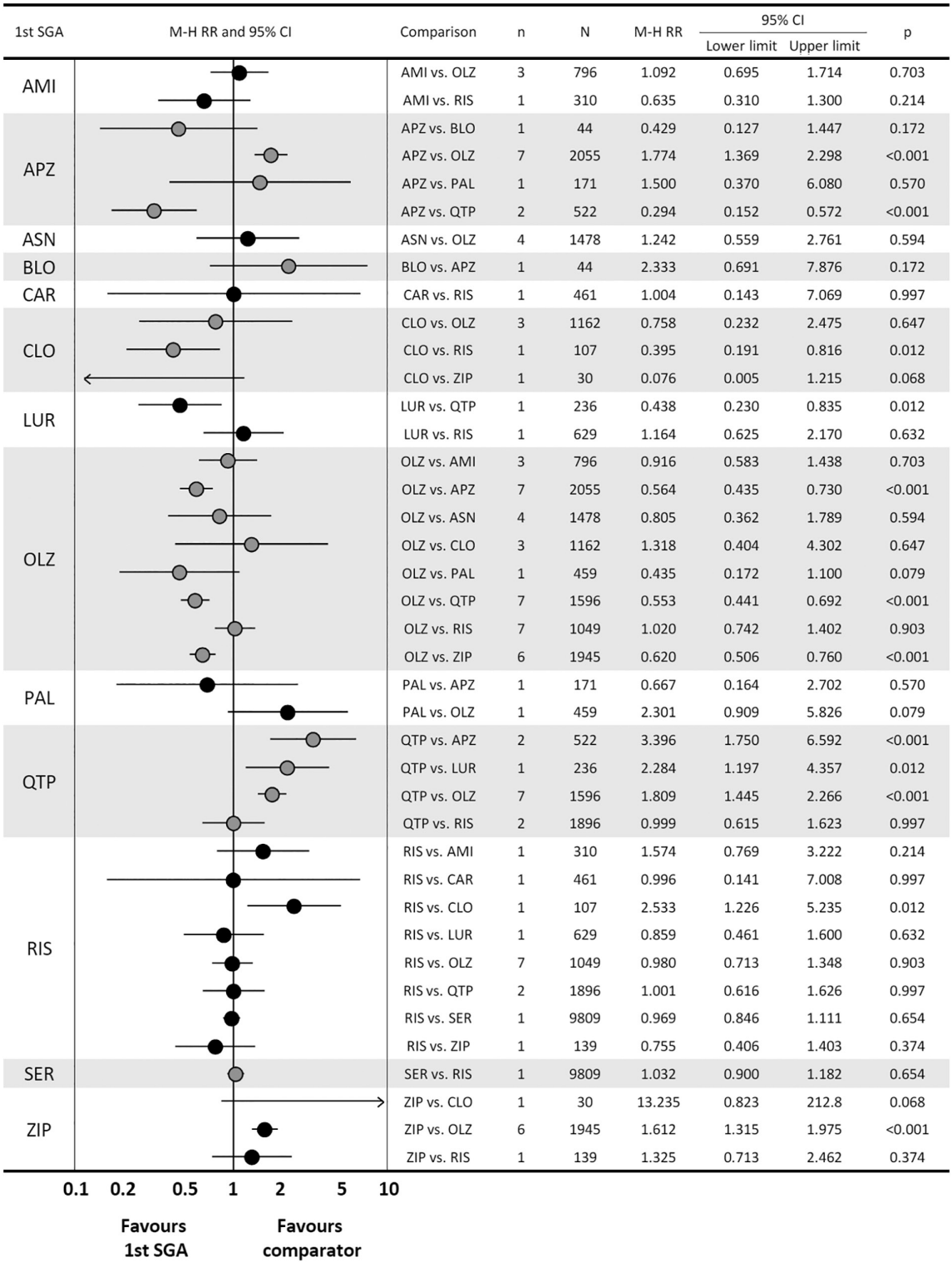
1st SGA	Comparison	n	N	SMD	95% CI		p
					Lower limit	Upper limit	
AMI	AMI vs. OLZ	3	791	0.077	-0.064	0.219	0.285
	AMI vs. QTP	1	208	0.241	-0.032	0.514	0.084
	AMI vs. RIS	1	244	-0.037	-0.288	0.214	0.774
	AMI vs. ZIP	1	186	0.049	-0.240	0.339	0.739
APZ	APZ vs. BLO	1	41	0.309	-0.308	0.927	0.326
	APZ vs. OLZ	2	628	0.143	-0.014	0.299	0.074
	APZ vs. PAL	1	134	1.108	0.743	1.472	<0.001
	APZ vs. QTP	2	488	-0.259	-0.497	-0.020	0.034
	APZ vs. ZIP	2	264	-0.309	-0.552	-0.066	0.013
ASN	ASN vs. OLZ	3	974	0.105	-0.024	0.233	0.110
BLO	BLO vs. APZ	1	41	-0.309	-0.927	0.308	0.326
CAR	CAR vs. RIS	1	456	-0.173	-0.357	0.011	0.066
CLO	CLO vs. OLZ	3	191	-0.081	-0.464	0.302	0.678
	CLO vs. QTP	1	41	-0.900	-1.696	-0.103	0.027
	CLO vs. RIS	3	121	-0.739	-1.476	-0.003	0.049
LUR	LUR vs. QTP	1	204	-0.401	-0.691	-0.111	0.007
	LUR vs. RIS	1	608	0.105	-0.065	0.274	0.227
OLZ	OLZ vs. AMI	3	791	-0.077	-0.219	0.064	0.285
	OLZ vs. APZ	2	628	-0.143	-0.299	0.014	0.074
	OLZ vs. ASN	3	974	-0.105	-0.233	0.024	0.110
	OLZ vs. CLO	3	191	0.081	-0.302	0.464	0.678
	OLZ vs. PAL	1	459	-0.200	-0.384	-0.017	0.032
	OLZ vs. QTP	5	661	-0.086	-0.326	0.154	0.482
	OLZ vs. RIS	9	1144	-0.168	-0.329	-0.007	0.041
	OLZ vs. ZIP	2	716	-0.194	-0.544	0.157	0.279
PAL	PAL vs. APZ	1	134	-1.108	-1.472	-0.743	<0.001
	PAL vs. OLZ	1	459	0.200	0.017	0.384	0.032
	PAL vs. ZIP	1	132	-1.331	-1.709	-0.954	<0.001
QTP	QTP vs. AMI	1	208	-0.241	-0.514	0.032	0.084
	QTP vs. APZ	2	488	0.259	0.02	0.497	0.034
	QTP vs. CLO	1	41	0.900	0.103	1.696	0.027
	QTP vs. LUR	1	204	0.401	0.111	0.691	0.007
	QTP vs. OLZ	5	661	0.086	-0.154	0.326	0.482
	QTP vs. RIS	6	1563	-0.029	-0.258	0.200	0.804
	QTP vs. ZIP	2	293	-0.164	-0.395	0.066	0.162
RIS	RIS vs. AMI	1	244	0.037	-0.214	0.288	0.774
	RIS vs. CAR	1	456	0.173	-0.011	0.357	0.066
	RIS vs. CLO	3	121	0.739	0.003	1.476	0.049
	RIS vs. LUR	1	608	-0.105	-0.274	0.065	0.227
	RIS vs. OLZ	9	1144	0.168	0.007	0.329	0.041
	RIS vs. QTP	6	1563	0.029	-0.200	0.258	0.804
ZIP	ZIP vs. AMI	1	186	-0.049	-0.339	0.240	0.739
	ZIP vs. APZ	2	264	0.309	0.066	0.552	0.013
	ZIP vs. OLZ	2	716	0.194	-0.157	0.544	0.279
	ZIP vs. PAL	1	132	1.331	0.954	1.709	<0.001
	ZIP vs. QTP	2	293	0.164	-0.066	0.395	0.162

Figure 3 Results of comparisons of psychopathology scores in meta-analysis of second-generation antipsychotics (SGAs). The first drug is the one written on the left side of the graph, and the comparator is written in the row of comparison. AMI – amisulpride, APZ – aripiprazole, ASN – asenapine, BLO – blonanserin, CAR – cariprazine, CLO – clozapine, LUR – lurasidone, OLZ – olanzapine, PAL – paliperidone, QTP – quetiapine, RIS – risperidone, SER – sertindole, ZIP – ziprasidone, SMD – standardized mean difference.



1st SGA	Comparison	n	N	M-H RR	95% CI		p
					Lower limit	Upper limit	
AMI	AMI vs. OLZ	3	796	1.396	0.811	2.403	0.228
	AMI vs. QTP	1	208	6.000	1.377	26.15	0.017
	AMI vs. RIS	1	310	1.091	0.617	1.931	0.764
	AMI vs. ZIP	1	186	1.352	0.557	3.279	0.505
APZ	APZ vs. BLO	1	44	1.250	0.386	4.046	0.710
	APZ vs. OLZ	7	2105	1.131	0.901	1.420	0.289
	APZ vs. PAL	1	171	0.900	0.302	2.680	0.850
	APZ vs. QTP	2	522	0.877	0.369	2.086	0.767
	APZ vs. ZIP	2	313	0.879	0.117	6.627	0.900
ASN	ASN vs. OLZ	4	1478	1.601	0.904	2.833	0.106
BLO	BLO vs. APZ	1	44	0.800	0.247	2.589	0.710
CAR	CAR vs. RIS	1	461	0.884	0.513	1.521	0.656
CLO	CLO vs. OLZ	3	1162	1.225	0.821	1.828	0.320
	CLO vs. QTP	1	64	0.510	0.138	1.890	0.314
	CLO vs. RIS	2	172	7.567	1.016	56.38	0.048
	CLO vs. ZIP	1	30	5.143	1.328	19.92	0.018
LUR	LUR vs. QTP	1	236	1.407	0.455	4.351	0.553
	LUR vs. RIS	1	629	1.481	0.955	2.296	0.079
OLZ	OLZ vs. AMI	3	796	0.716	0.416	1.232	0.228
	OLZ vs. APZ	7	2105	0.884	0.704	1.110	0.289
	OLZ vs. ASN	4	1478	0.625	0.353	1.106	0.106
	OLZ vs. CLO	3	1162	0.816	0.547	1.218	0.320
	OLZ vs. PAL	1	459	0.494	0.174	1.399	0.184
	OLZ vs. QTP	8	1942	0.925	0.582	1.469	0.741
	OLZ vs. RIS	14	2610	1.080	0.811	1.439	0.597
	OLZ vs. ZIP	6	1945	0.827	0.573	1.194	0.311
PAL	PAL vs. APZ	1	171	1.111	0.373	3.308	0.850
	PAL vs. OLZ	1	459	2.025	0.715	5.736	0.184
	PAL vs. ZIP	1	164	3.074	0.639	14.79	0.161
QTP	QTP vs. AMI	1	208	0.167	0.038	0.726	0.017
	QTP vs. APZ	2	522	1.140	0.479	2.712	0.767
	QTP vs. CLO	1	64	1.960	0.529	7.259	0.314
	QTP vs. LUR	1	236	0.711	0.230	2.197	0.553
	QTP vs. OLZ	8	1942	1.081	0.681	1.717	0.741
	QTP vs. RIS	7	3147	1.265	1.064	1.505	0.008
	QTP vs. ZIP	4	1064	0.717	0.381	1.352	0.304
RIS	RIS vs. AMI	1	310	0.916	0.518	1.621	0.764
	RIS vs. CAR	1	461	1.131	0.657	1.948	0.656
	RIS vs. CLO	2	172	0.132	0.018	0.985	0.048
	RIS vs. LUR	1	629	0.675	0.436	1.047	0.079
	RIS vs. OLZ	14	2610	0.926	0.695	1.232	0.597
	RIS vs. QTP	7	3147	0.790	0.665	0.940	0.008
	RIS vs. SER	1	9809	0.496	0.428	0.575	<0.001
	RIS vs. ZIP	3	906	0.704	0.489	1.013	0.059
SER	SER vs. RIS	1	9809	2.016	1.738	2.338	<0.001
ZIP	ZIP vs. AMI	1	186	0.740	0.305	1.795	0.505
	ZIP vs. APZ	2	313	1.138	0.151	8.577	0.900
	ZIP vs. CLO	1	30	0.194	0.050	0.753	0.018
	ZIP vs. OLZ	6	1945	1.209	0.838	1.746	0.311
	ZIP vs. PAL	1	164	0.325	0.068	1.565	0.161
	ZIP vs. QTP	4	1064	1.394	0.740	2.628	0.304
	ZIP vs. RIS	3	906	1.420	0.987	2.044	0.059

Figure 4 Results of comparisons of intolerability-related discontinuation in meta-analysis of second-generation antipsychotics (SGAs). The first drug is the one written on the left side of the graph, and the comparator is written in the row of comparison. AMI – amisulpride, APZ – aripiprazole, ASN – asenapine, BLO – blonanserin, CAR – cariprazine, CLO – clozapine, LUR – lurasidone, OLZ – olanzapine, PAL – paliperidone, QTP – quetiapine, RIS – risperidone, SER – sertindole, ZIP – ziprasidone, M-H RR – Mantel-Haenszel risk ratio.



1st SGA	Comparison	n	N	M-H RR	95% CI		p
					Lower limit	Upper limit	
AMI	AMI vs. OLZ	3	796	1.092	0.695	1.714	0.703
	AMI vs. RIS	1	310	0.635	0.310	1.300	0.214
APZ	APZ vs. BLO	1	44	0.429	0.127	1.447	0.172
	APZ vs. OLZ	7	2055	1.774	1.369	2.298	<0.001
	APZ vs. PAL	1	171	1.500	0.370	6.080	0.570
	APZ vs. QTP	2	522	0.294	0.152	0.572	<0.001
ASN	ASN vs. OLZ	4	1478	1.242	0.559	2.761	0.594
BLO	BLO vs. APZ	1	44	2.333	0.691	7.876	0.172
CAR	CAR vs. RIS	1	461	1.004	0.143	7.069	0.997
CLO	CLO vs. OLZ	3	1162	0.758	0.232	2.475	0.647
	CLO vs. RIS	1	107	0.395	0.191	0.816	0.012
	CLO vs. ZIP	1	30	0.076	0.005	1.215	0.068
LUR	LUR vs. QTP	1	236	0.438	0.230	0.835	0.012
	LUR vs. RIS	1	629	1.164	0.625	2.170	0.632
OLZ	OLZ vs. AMI	3	796	0.916	0.583	1.438	0.703
	OLZ vs. APZ	7	2055	0.564	0.435	0.730	<0.001
	OLZ vs. ASN	4	1478	0.805	0.362	1.789	0.594
	OLZ vs. CLO	3	1162	1.318	0.404	4.302	0.647
	OLZ vs. PAL	1	459	0.435	0.172	1.100	0.079
	OLZ vs. QTP	7	1596	0.553	0.441	0.692	<0.001
	OLZ vs. RIS	7	1049	1.020	0.742	1.402	0.903
	OLZ vs. ZIP	6	1945	0.620	0.506	0.760	<0.001
PAL	PAL vs. APZ	1	171	0.667	0.164	2.702	0.570
	PAL vs. OLZ	1	459	2.301	0.909	5.826	0.079
QTP	QTP vs. APZ	2	522	3.396	1.750	6.592	<0.001
	QTP vs. LUR	1	236	2.284	1.197	4.357	0.012
	QTP vs. OLZ	7	1596	1.809	1.445	2.266	<0.001
	QTP vs. RIS	2	1896	0.999	0.615	1.623	0.997
RIS	RIS vs. AMI	1	310	1.574	0.769	3.222	0.214
	RIS vs. CAR	1	461	0.996	0.141	7.008	0.997
	RIS vs. CLO	1	107	2.533	1.226	5.235	0.012
	RIS vs. LUR	1	629	0.859	0.461	1.600	0.632
	RIS vs. OLZ	7	1049	0.980	0.713	1.348	0.903
	RIS vs. QTP	2	1896	1.001	0.616	1.626	0.997
	RIS vs. SER	1	9809	0.969	0.846	1.111	0.654
	RIS vs. ZIP	1	139	0.755	0.406	1.403	0.374
SER	SER vs. RIS	1	9809	1.032	0.900	1.182	0.654
ZIP	ZIP vs. CLO	1	30	13.235	0.823	212.8	0.068
	ZIP vs. OLZ	6	1945	1.612	1.315	1.975	<0.001
	ZIP vs. RIS	1	139	1.325	0.713	2.462	0.374

Figure 5 Results of comparisons of inefficacy-related discontinuation in meta-analysis of second-generation antipsychotics (SGAs). The first drug is the one written on the left side of the graph, and the comparator is written in the row of comparison. AMI – amisulpride, APZ – aripiprazole, ASN – asenapine, BLO – blonanserin, CAR – cariprazine, CLO – clozapine, LUR – lurasidone, OLZ – olanzapine, PAL – paliperidone, QTP – quetiapine, RIS – risperidone, SER – sertindole, ZIP – ziprasidone, M-H RR – Mantel-Haenszel risk ratio.

Table 2 Results of meta-analysis for adverse events

Outcome	Comparison	n	N	RR/SMD	95% CI		p	I^2 (%)
					Lower limit	Upper limit		
Akathisia	ASN vs. OLZ	1	89	–0.21	–2.00	1.58	0.818	–
	CAR vs. RIS	1	460	0.15	–0.18	0.49	0.361	–
	CLO vs. OLZ	1	58	0.44	–1.26	2.14	0.614	–
	CLO vs. QTP	1	54	–0.97	–2.03	0.08	0.071	–
	CLO vs. RIS	1	54	0.30	–1.41	2.00	0.735	–
	LUR vs. RIS	1	608	0.13	–0.04	0.30	0.131	–
	OLZ vs. QTP	2	201	–0.46	–1.66	0.75	0.459	**51.2**
	OLZ vs. RIS	3	548	–0.08	–0.32	0.17	0.552	17.2
	OLZ vs. ZIP	2	725	–0.11	–0.28	0.05	0.184	0.0
	QTP vs. RIS	3	1277	0.16	–0.56	0.89	0.657	**65.4**
	QTP vs. ZIP	1	190	0.26	–0.42	0.93	0.458	–
	RIS vs. ZIP	1	193	–0.17	–0.97	0.64	0.683	–
Dyskinesia	AMI vs. OLZ	1	356	–0.11	–0.32	0.09	0.281	–
	AMI vs. RIS	1	310	0.02	–0.21	0.24	0.886	–
	ASN vs. OLZ	1	89	–1.46	–3.25	0.33	0.109	–
	CLO vs. OLZ	2	88	–0.21	–0.71	0.29	0.416	0.0
	CLO vs. QTP	1	44	0.47	–0.76	1.69	0.456	–
	CLO vs. RIS	1	45	1.01	–0.61	2.64	0.222	–
	OLZ vs. QTP	3	234	–0.35	–0.76	0.07	0.099	0.0
	OLZ vs. RIS	7	698	–0.02	–0.19	0.15	0.790	0.0
	OLZ vs. ZIP	2	701	–0.03	–0.19	0.13	0.726	0.0
	QTP vs. RIS	4	1,301	0.23	–0.28	0.74	0.375	**58.8**
	QTP vs. ZIP	1	165	**0.52**	**0.05**	**0.99**	**0.030**	–
	RIS vs. ZIP	1	156	0.10	–0.44	0.65	0.709	–
Parkinsonism	AMI vs. OLZ	2	562	0.26	–0.34	0.86	0.399	77.6
	AMI vs. QTP	1	179	0.30	–0.18	0.79	0.219	–
	AMI vs. RIS	1	310	0.07	–0.15	0.29	0.539	–
	AMI vs. ZIP	1	162	0.03	–0.43	0.50	0.887	–
	APZ vs. BLO	1	44	–0.41	–1.74	0.92	0.546	–
	APZ vs. OLZ	3	1,483	0.06	–0.27	0.38	0.737	**76.5**
	APZ vs. QTP	2	497	–0.10	–0.45	0.25	0.585	26.6
	APZ vs. ZIP	1	124	–0.07	–0.57	0.43	0.776	–
	ASN vs. OLZ	2	529	0.08	–0.90	1.06	0.867	16.0
	CAR vs. RIS	1	460	–0.23	–0.61	0.15	0.233	–
	CLO vs. OLZ	3	201	0.13	–0.18	0.45	0.402	0.0
	CLO vs. QTP	1	53	–0.75	–1.90	0.40	0.200	–
	CLO vs. RIS	1	54	0.30	–1.41	2.00	0.735	–
	LUR vs. RIS	1	621	–0.19	–0.46	0.08	0.169	–
	OLZ vs. QTP	5	1,126	–0.08	–0.51	0.36	0.725	**51.7**
	OLZ vs. RIS	9	1,934	**–0.28**	**–0.44**	**–0.12**	**0.001**	28.3
	OLZ vs. ZIP	5	1,808	–0.10	–0.23	0.03	0.129	0.0
	QTP vs. RIS	4	1,953	–0.26	–0.60	0.08	0.133	**60.5**

Table 2 Results of meta-analysis for adverse events (*continued*)

Outcome	Comparison	n	N	RR/SMD	95% CI		p	I^2 (%)
					Lower limit	Upper limit		
	QTP vs. ZIP	4	971	–0.19	–0.55	0.18	0.323	44.1
	RIS vs. ZIP	2	725	0.40	–0.23	1.03	0.214	**66.6**
Body weight gain	AMI vs. OLZ	3	742	**–0.40**	**–0.54**	**–0.25**	**<0.001**	0.0
	AMI vs. QTP	1	127	–0.06	–0.41	0.29	0.749	–
	AMI vs. RIS	1	195	**–0.46**	**–0.83**	**–0.10**	**0.013**	–
	AMI vs. ZIP	1	115	0.36	–0.02	0.74	0.066	–
	APZ vs. OLZ	5	1,413	**–0.63**	**–0.81**	**–0.44**	**<0.001**	31.7
	APZ vs. PAL	1	134	**0.37**	**0.03**	**0.71**	**0.034**	–
	APZ vs. QTP	2	501	–0.06	–0.47	0.35	0.774	**53.5**
	APZ vs. ZIP	2	264	0.63	–0.07	1.32	0.077	**82.3**
	APZ vs. BLO	1	44	0.09	–0.50	0.68	0.770	–
	ASN vs. OLZ	4	1,447	–0.39	–0.86	0.08	0.107	**88.0**
	CAR vs. RIS	1	431	**–0.29**	**–0.48**	**–0.10**	**0.003**	–
	CLO vs. OLZ	4	1,167	–0.33	–0.80	0.13	0.161	**83.0**
	CLO vs. QTP	1	54	0.02	–0.61	0.64	0.957	–
	CLO vs. RIS	3	96	–0.32	–0.78	0.14	0.172	0.0
	LUR vs. QTP	1	111	–0.13	–0.54	0.28	0.526	–
	LUR vs. RIS	1	621	**–0.48**	**–0.65**	**–0.31**	**<0.001**	–
	OLZ vs. PAL	1	449	**0.49**	**0.31**	**0.68**	**<0.001**	–
	OLZ vs. QTP	8	1,592	**0.42**	**0.21**	**0.62**	**<0.001**	**69.1**
	OLZ vs. RIS	11	1,646	**0.37**	**0.19**	**0.55**	**<0.001**	**58.5**
	OLZ vs. ZIP	6	1,509	**0.74**	**0.62**	**0.85**	**<0.001**	9.6
	PAL vs. ZIP	1	132	**0.62**	**0.27**	**0.97**	**0.001**	–
	QTP vs. RIS	8	2,813	0.01	–0.06	0.09	0.701	0.0
	QTP vs. ZIP	4	871	**0.24**	**0.10**	**0.38**	**0.001**	0.0
	RIS vs. SER	1	9,809	–0.61	–2.37	1.16	0.501	–
	RIS vs. ZIP	3	800	**0.22**	**0.07**	**0.37**	**0.003**	0.0
Prolactin increase	AMI vs. OLZ	1	105	**0.63**	**0.24**	**1.03**	**0.002**	–
	AMI vs. QTP	1	84	**0.62**	**0.18**	**1.07**	**0.006**	–
	AMI vs. ZIP	1	71	**1.05**	**0.53**	**1.57**	**<0.001**	–
	APZ vs. OLZ	4	1,686	**–1.09**	**–1.63**	**–0.54**	**<0.001**	**84.4**
	APZ vs. QTP	1	382	–0.23	–1.83	1.38	0.783	–
	ASN vs. OLZ	1	89	0.07	–0.47	0.61	0.804	–
	CLO vs. OLZ	1	55	–0.29	–0.87	0.30	0.333	–
	CLO vs. QTP	1	52	0.39	–0.24	1.02	0.229	–
	CLO vs. RIS	1	50	**–1.62**	**–2.36**	**–0.88**	**<0.001**	–
	LUR vs. RIS	1	554	**–0.56**	**–0.74**	**–0.38**	**<0.001**	–
	OLZ vs. QTP	6	996	**0.13**	**0.01**	**0.26**	**0.040**	0.0
	OLZ vs. RIS	7	1,225	**–1.05**	**–1.23**	**–0.87**	**<0.001**	40.7
	OLZ vs. ZIP	5	1,510	0.06	–0.16	0.27	0.596	**73.1**
	QTP vs. RIS	8	2,131	**–1.24**	**–1.59**	**–0.90**	**<0.001**	**84.9**
	QTP vs. ZIP	3	659	0.03	–0.41	0.47	0.890	**82.9**

Table 2 Results of meta-analysis for adverse events (*continued*)

Outcome	Comparison	n	N	RR/SMD	95% CI		p	I^2 (%)
					Lower limit	Upper limit		
	RIS vs. SER	1	9,809	0.00	–0.88	0.88	1.000	–
	RIS vs. ZIP	2	596	**0.93**	**0.75**	**1.10**	**<0.001**	0.0
Sedation and/or somnolence	AMI vs. OLZ	1	377	0.99	0.46	2.16	0.989	–
	AMI vs. RIS	1	310	0.69	0.29	1.65	0.407	–
	APZ vs. BLO	1	44	0.50	0.05	5.12	0.559	–
	APZ vs. OLZ	5	1,802	0.64	0.38	1.09	0.099	**68.0**
	APZ vs. QTP	1	119	1.39	0.60	3.24	0.442	–
	APZ vs. ZIP	1	124	1.34	0.60	3.00	0.479	–
	ASN vs. OLZ	3	1,038	0.89	0.66	1.22	0.477	0.0
	CAR vs. RIS	1	460	0.69	0.30	1.59	0.385	–
	CLO vs. OLZ	1	956	**1.86**	**1.54**	**2.23**	**<0.001**	–
	CLO vs. RIS	1	14	5.00	0.77	32.57	0.092	–
	LUR vs. RIS	1	621	0.76	0.52	1.12	0.166	–
	OLZ vs. PAL	1	459	**2.85**	**1.29**	**6.31**	**0.010**	–
	OLZ vs. QTP	4	1,220	0.95	0.83	1.10	0.531	0.0
	OLZ vs. RIS	7	1,656	1.14	0.99	1.32	0.064	0.0
	OLZ vs. ZIP	2	766	1.78	0.84	3.75	0.130	**79.5**
	QTP vs. RIS	6	3,095	**1.46**	**1.09**	**1.96**	**0.010**	**78.1**
	QTP vs. ZIP	3	861	1.49	0.89	2.48	0.129	**56.7**
	RIS vs. ZIP	3	906	1.35	0.94	1.95	0.104	41.4

Significant ($p<0.05$) results are in bold prints. RR – risk ratio, SMD – standardized mean difference, AMI – amisulpride, APZ – aripiprazole, ASN – asenapine, BLO – blonanserin, CAR – cariprazine, CLO – clozapine, LUR – lurasidone, OLZ – olanzapine, PAL – paliperidone, QTP – quetiapine, RIS – risperidone, SER – sertindole, ZIP – ziprasidone. Effect sizes for sedation and/or somnolence are expressed in RR, others in SMD. SMD <0 and RR<1 indicate superiority of the first medication.

DISCUSSION

In this first comprehensive meta-analysis of comparative effectiveness, efficacy and tolerability of SGAs in the long-term treatment of schizophrenia, including 59 studies and 45,787 participants, no consistent superiority of any single antipsychotic across multiple outcome domains was observed.

Regarding all-cause discontinuation, clozapine, olanzapine and risperidone were superior to several other SGAs, whereas quetiapine was inferior to several other SGAs. Regarding psychopathology, clozapine and olanzapine were superior to several other SGAs, while again quetiapine as well as ziprasidone were inferior to several other SGAs. Regarding functioning, QOL and remission, data were sparse.

Regarding intolerability-related discontinuation, risperidone was superior and clozapine was inferior to several other SGAs. However, it should be kept in mind that discontinuation due to adverse events often includes inefficacy-related adverse events in modern trials and, therefore, this outcome does not purely reflect tolerability.

When broken down into individual adverse events, superiority/inferiority patterns became clearer in some domains. For example, olanzapine was associated with more body weight gain than all other non-clozapine SGAs, whereas ziprasidone was less so than other SGAs; and amisulpride and risperidone raised serum prolactin level more than other SGAs. Furthermore, sedation and/or somnolence were more common during long-term treatment with clozapine and quetiapine.

We focused on head-to-head comparisons for the current meta-analysis. The relative lack of direct head-to-head maintenance comparisons may raise interest in conducting a network meta-analysis. However, while such methodology using indirect comparisons can create rankings, the very lack of so many comparisons and the heterogeneity of the studies conducted in different populations and over several decades are likely to introduce relevant biases that are not present in meta-analyses of direct head-to-head trials[9].

In fact, comparing our results with those from Zhao et al[85], who conducted a network meta-analysis of relapse prevention studies in stable patients with schizophrenia that also included first-generation and long-acting injectable antipsychotics, some differences emerge. For example, for relapse prevention, the only significant result involving an SGA was olanzapine's superiority over chlorpromazine and haloperidol, whereas we found olanzapine to be superior to risperidone (although based on one trial only). Furthermore, regarding all-cause discontinuation, we

observed a significant superiority of olanzapine over aripiprazole, paliperidone, quetiapine, risperidone and ziprasidone in direct comparisons, while Zhao et al, including indirect comparisons, found olanzapine only superior to aripiprazole. Thus, we believe that restricting the meta-analysis exclusively to randomized head-to-head comparisons yields more precise results.

What are the implications of our findings for the choice of SGA in the long-term treatment of schizophrenia? First, we must consider the magnitude of the effect sizes for all-cause discontinuation. Since these ranged from medium to large, we believe that they are clinically meaningful, especially during the important maintenance treatment phase[2,7,86,87]. The results regarding psychopathology roughly matched the findings for all-cause discontinuation, in that clozapine and olanzapine were superior to several other SGAs, whereas quetiapine seemed inferior, this time together with ziprasidone. However, the findings of divergent adverse effect outcomes, with particular disadvantages for clozapine, olanzapine and risperidone, highlight the fact that it is crucial to not view efficacy and effectiveness in isolation of tolerability. For example, clozapine and olanzapine are among the medications with some of the most problematic adverse effects, including weight gain and metabolic abnormalities[10,88] as well as, in the case of clozapine, blood dyscrasias[89]. Given such inconsistent results in the different outcome categories, the importance of a balanced medication choice based on each patient's own situation should be emphasized.

Regarding the comparative effectiveness of clozapine and olanzapine, we found similar results in the maintenance treatment of schizophrenia. Even in studies targeting treatment-refractory patients, the effect sizes were similar. Since a network meta-analysis of short-term trials in refractory patients did not find superiority of clozapine vs. olanzapine, risperidone and ziprasidone[90], which may have been driven by use of suboptimal clozapine doses or inclusion of non-refractory patients, further high-quality, short- and long-term, head-to-head trials of clozapine vs. other SGAs are needed.

Several limitations of this study need to be considered. Most comparisons relied on relatively few head-to-head trials. As many as 139 of all 250 comparisons were based on one study only, but we only meta-analyzed outcomes for which at least two head-to-head trials provided data. The number of patients per trial was also often small, and dose equivalencies used across studies might not have been balanced or consistent. Furthermore, the limited number of studies reduced the power of our exploratory subgroup analyses. Additionally, only six and eleven studies reported remission and relapse as an outcome, respectively. However, since psychopathology, treatment response and functioning can worsen with repeated relapse[87,91], information on comparative remission and relapse risk with individual antipsychotics is important.

The randomization point in the included studies differed, i.e., some studies randomized patients during the acute phase, and others during the maintenance phase. Moreover, some studies included exclusively treatment-refractory patients, whereas some others included exclusively first-episode patients. Relapse and remission definitions varied across studies. Moreover, two of the included studies had an enriched design, and two allowed switches after randomization, which could have affected the results. Such heterogeneity of the study design as well as patient populations introduces biases. However, we assessed the impact of patient and study design characteristics as potential moderators by conducting subgroup analyses.

Finally, although the effectiveness of long-acting injectable antipsychotics (LAIs) in the long-term treatment of schizophrenia is clearly important[92], we excluded LAI studies, as this aspect has already been comprehensively meta-analyzed[13,14,93]. Including LAIs in this meta-analysis, which are not available for all SGAs, would have further increased the heterogeneity of samples and methods, the complexity of the analyses and the interpretation of the results.

In conclusion, results from this meta-analysis suggest that there are some significant differences in the effectiveness, efficacy and tolerability among SGAs in the long-term treatment of schizophrenia. Clozapine, olanzapine and risperidone seem to be superior to several other SGAs regarding all-cause discontinuation, while quetiapine seems to be inferior. Regarding psychopathology scores, clozapine and olanzapine seem to be superior to several other SGAs, while quetiapine and ziprasidone seem to be less effective. Regarding discontinuation due to adverse events, only risperidone was superior and clozapine was inferior to several other SGAs.

Due to the limited number of head-to-head trials, the comparative effectiveness of some SGAs is unclear, and results need to be interpreted cautiously whenever they were based on few trials. Thus, a sufficiently larger database involving many SGAs and including detailed effectiveness and tolerability outcomes is desirable to further guide the evidence-based long-term treatment of patients with schizophrenia. In particular, identifying predictors of beneficial outcomes with specific antipsychotics would further enhance the ability to personalize treatments.

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The modern unconscious

Psychology, as a scientific enterprise, began by using the simplest method of all: self-reports. To study the nature of conscious experiences, just ask people about those experiences. But this soon ran into a problem. The methods used to study conscious thought were unreliable: one subject's introspection about a sensory experience was not the same as another subject's. Fed up with this lack of replicability, the scientific establishment in the form of J. Watson[1] threw out the study of the conscious mind as unscientific. Instead, he said, the task of psychology should be to manipulate the external stimulus environment and objectively measure the subject's responses, without recourse to any internal "black box" of mental activity.

Behaviorists thus sacrificed the richness and complexity of human psychology in return for a greatly simplified version for which they had reliable methods to study. And, because the mind no longer mattered, they could study the much more convenient rat or pigeon instead of actual humans. But worst of all, over time, behaviorists came to confuse the lack of available reliable methods to study human mental life with the lack of any causal role played by mental life[2].

It was only with the cognitive revolution of the 1960s that mental processes once again became a legitimate topic of study in scientific human psychology. And a major reason for the cognitive revolution was that technology had developed sufficiently to permit accurate and replicable methods. Now that the methods existed to study mental processes, mental processes themselves existed again.

At about the same time as Watson published his Behaviorist Manifesto, S. Freud was publishing his analyses of the human unconscious mind. Freud and his contemporary P. Janet were medical scientists who studied patients with distressing ailments for which no physical cause could be found. A prevalent viewpoint of that era was that these abnormal emotional and behavioral syndromes were supernaturally caused, such as by demonic possession[3]. As medical scientists, however, Freud and Janet believed in physical causes and proposed that a separate unconscious mind was the culprit. In effect, they took the metaphysical demons and located them inside the patient's physical head.

Here again, though, a methodological error was made. Although Janet cautioned that the notion of a separate unconscious mind should apply only to those abnormal cases, Freud insisted that it held for all human beings[4]. The error was to generalize from a (small) sample of abnormal functioning to the normal, everyday mental life of everyone. But, as we know, Freud's position won the day.

There was a second problem with Freud's theory. The issue was falsifiability. For scientific progress to be made, K. Popper[5] argued, a good theory had to be falsifiable – it had to be capable of generating hypotheses that could be put to the test and possibly found wrong.

There is a lamentable tendency in scientific practice to dismiss a flawed approach as completely wrong – thereby throwing out the worthwhile baby with the worthless bathwater. Many today dismiss the very notion of unconscious influences merely because Freud's theory was unfalsifiable and based on abnormal cases. And cognitive psychology threw out behaviorism and with it the idea that the external environment could cause human choices and behavior[6]. But of course there is a third alternative to a theory being either entirely correct or entirely incorrect.

Like the three blind men reporting on the elephant, all three of the grand psychological theories of the past century contained a profound truth regarding human nature, but none by itself gave the complete picture. The elegance of the modern research on unconscious processes is that it combines the best of these three major psychological theories. What this research reveals is that many important affective, motivational and behavioral phenomena operate without the person's awareness or conscious intention (Freud); that they are often triggered by events, people, situational settings, and other external stimuli (behaviorism); but that these external stimuli exert their effect through their automatic activation of internal mental representations and processes (cognitive psychology).

This research enterprise has the additional advantage of overcoming the methodological problems of the earlier work. It studies the behavior and psychological reactions of average human beings (not clinical patients, or rats or pigeons) in everyday situations, with the participants randomly assigned to experimental conditions, and through the generation and testing of falsifiable hypotheses.

What have we learned from this research? The two main conclusions are that there are several different sources of unconscious influence over choices and behavior, and that they are generated from the same, single mind that produces conscious influences.

The dominant assumption of cognitive psychology in the 1970s was that the higher mental processes were almost entirely under conscious, executive control[7]. But, as the research progressed from 1980 onwards, the role of unconscious processes in everyday life was revealed to be far greater than anyone ever suspected.

The behavioral data in social and motivational psychology consistently pointed to unconscious processes having the same signature characteristics and operating features as when those processes were engaged in consciously. This was confirmed by brain imaging studies showing that the same brain regions – reactive to the presence of reward and incentive, for example, or involved in computations in complex decision-making – were active whether the person was aware of the process operating or not. There is a single mind, and it can operate in either conscious or unconscious mode.

The main mechanisms of unconscious influence come from the past, the present, and the future[8]. From the past are deep and primary motivations from our evolutionary heritage, such as for survival and safety, resource acquisition, reproduction and social bonding. Recent research has shown how even

abstract social attitudes, such as conservative vs. liberal ideologies, and attitudes towards immigration, are influenced by these deeply rooted motivations.

But one's own personal past – namely, early childhood experiences of which one has no memory as an adult – also exerts its unconscious influence. Longitudinal studies of infants whose degree of attachment and bonding to the mother were measured when they were 1 year old show that this measure predicted how many friends they had in high school, and how often their close romantic relationships broke up in their 20s.

In the present, the behavior and emotions of those around us are contagious to us. This effect is now even more pronounced thanks to social media and electronic social networks. People we don't even know affect us in important ways, such as in contributing to the development of obesity and depression.

And how can the future affect us unconsciously if it hasn't happened yet? Because our minds are capable of time travel, and spend a good deal of time in the future. Our current goals for future outcomes color how we see the present – without realizing it, what is good for the goal becomes what we consider good for us, even if it runs against our core values and identity. On the more positive side, our important goals are capable of operating in the background while our conscious mind is elsewhere, a phenomenon which many famous writers and scientists have noted was a boon to their creativity and insights.

Psychology may be a young science, but it has already been blessed with the lifelong efforts of some very deep thinkers. In hindsight, none of them were entirely right, but neither were they entirely wrong. It is by combining their collective wisdom that we can reach a more complete and accurate account of the human mind, including the sophisticated and adaptive ways it operates unconsciously.

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Acceptance and commitment therapy: towards a unified model of behavior change

Well-established research programs should be evaluated relative to progress toward their stated purposes. The 35-year old program of development of acceptance and commitment therapy (ACT; said as a word, not initials) has followed an unusually lengthy strategy that was dictated by its ambitious goal: the creation of a unified process-based model of how to alleviate human psychological problems and promote behavioral effectiveness[1].

Instead of generating and refining a technologically-defined protocol for the treatment of specific syndromes, ACT research has from the beginning been based on an alternative vision more characteristic of its roots in behavior analysis and early behavior therapy: namely, the aspiration to identify change processes that facilitate psychological development based on principles that have high precision and scope of application, and depth across levels of analysis.

The resulting body of work now spans more than 2,000 studies, including research on ACT outcomes; research on the psychological flexibility model that underlies ACT (and its primary psychological change processes of acceptance, cognitive defusion, flexible attention to the now, a transcendent sense of self, values, and committed action); and work on relational frame theory (the analysis of human cognition that adds needed symbolic learning principles to the existing behavioral and evolution science principles on which this entire "contextual behavioral science" program stands[1]).

There are currently over 280 randomized controlled trials of ACT, involving nearly 33,000 participants (see bit.ly/ACTRCTs), in virtually every major area of mental and behavioral health, and many social and recreational areas as well[2]; over 60 mediational studies; scores of component studies[3]; assessment devices ranging from implicit measures to overt behavioral measures, in all of the process areas delineated by the research program; longitudinal studies on flexibility processes as long as a decade; and treatment studies with follow-ups as long as five years. Approximately 90% of the existing research base has appeared in the last decade. There are currently 40 meta-analyses of this literature, including eleven in the last year alone.

Characterizing a rapidly expanding literature with broad conclusions is risky, because any specific statement may have one or two exceptions, but I believe that a fair reading of these studies supports the following conclusions.

First, ACT outcomes are as good, or in some cases better, than alternative evidence-based approaches designed to target specific areas of mental and behavioral health (anxiety, depression, substance use, chronic pain, and so on), but they are produced by a single unified model of behavior change.

Second, ACT works largely by modifying psychological flexibility processes. When these processes are successfully modified by ACT methods, long-term positive outcomes follow, whether the domain being addressed is in traditional areas of psychopathology, behavioral aspects of physical health (diet,

exercise, coping with disease), social areas such as reducing prejudice and its impact, or positive outcomes in sport, business, leadership, relationships, and similar areas. ACT and psychological flexibility processes are now known to be relevant to a much broader range of human functioning than alleviation of mental health problems alone.

Third, ACT is a prime example of "process-based therapy" (PBT)[4,5], in which the intervention method is defined not by a protocol but by a practical model containing a limited set of evidence-based processes that are fitted to the needs of the individual, and a linked set of evidence-based kernels that can be deployed on a case-by-case basis to alter particular processes of change, so as to help individual clients meet their health and prosperity goals across a range of targets, beyond the meaning even of terms like "transdiagnostic". As such, ACT is a successful "proof of concept" of PBT, offering a more generally applicable alternative to the "protocols for syndromes" era that arguably is now passing away and that has dominated evidence-based psychological and psychiatric care over the last several decades.

Fourth, while ACT methods reliably alter psychological flexibility processes, as do some methods from other traditions, they fail to do so in a small set of contexts that are presently difficult to characterize. When ACT intervention kernels do *not* successfully alter flexibility processes, outcomes are hit and miss, suggesting the need for continued procedural development linked to the underlying process model.

Fifth, psychological flexibility processes form a coherent set, and outcomes are less positive if any are left behind. Psychological flexibility fosters healthy forms of variation (through acceptance and cognitive defusion), selection (through values), retention (through behavioral habits formed by the practice and pattern integration of committed action), and context sensitivity (through flexible attention to the now and the greater conscious awareness emerging from a transcendent sense of self), that target needed dimensions of development (affect; cognition; attention; motivation; self; overt behavior) at the right level of selection (sub-organismic; whole organism; small group).

Because of this focus on variation and selective retention in context at the right dimension and level, psychological flexibility provides a coherent set of skills needed for behavioral systems to evolve. It is helpful for forms of psychological care to fit within an extended evolutionary synthesis[6], because they can be combined with evolutionarily sensible processes at other levels of analysis to create programs of intentional change, such as combining individual change with the effort to evolve more prosocial groups[7]. If the ACT research program is determined to be successful, it thus indirectly supports the possible value of an integration of evolutionary science and behavioral science[8].

Sixth, ACT can be successfully delivered across a very wide range of settings (e.g., outpatient, inpatient), methods of delivery (e.g., online, books, apps, face to face), forms (e.g., groups, individual therapy, peer support), providers (e.g., nurses, occupational therapists, physical therapists, psychologists, psychiatrists), and systems of care (e.g., preventive, acute, aftercare). Robust ACT research programs exist in every area of the world, and the relationship of flexibility processes to health outcomes is similar across cultures, ethnicities, languages, and religious background.

Finally, relational frame theory is an evolutionarily sensible model of cognition that can be used to refine ACT methods[1], to derive additional change methods in psychotherapy directly[9], and to facilitate work in education, developmental disabilities, intellectual development in normal populations, implicit cognition, and many other applied areas of behavioral science[10].

In summary, as evaluated against its unusually ambitious goals, the ACT research program appears to be progressive. Much more remains to be done, but ACT has established itself as a viable form of evidence-based therapy, based on a unified model of behavior change grounded in evolutionary and contextual behavioral science principles.

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The need to investigate nocebo effects in more detail

While much discussion has focused on placebo effects over the past years, less attention has been paid to nocebo phenomena, in both clinical trials and medical practice[1-3]. Unfortunately, psychiatry is one of the disciplines in which we know the least about nocebo effects, although their involvement across a variety of mental disorders is likely to be very significant. Indeed, mental disorders are difficult to investigate in this respect, from both a clinical and a neuroscientific perspective, compared to conditions such as pain and motor disorders.

The nocebo effect represents the evil twin of the placebo effect, whereby the patient's negative expectations may lead to clinical worsening[1,2]. Therefore, it can provide important infor-

mation on the psychological factors involved in the generation and time course of a disease.

Although there are a number of clinical trials in psychiatry in which nocebo effects have been assessed and described, little information can be derived from these studies, as the possible psychological and neurobiological underpinnings are difficult to extrapolate. For example, in a meta-analysis of antidepressant clinical trials, high nocebo effects were found, yet the possible sources of these effects could not be identified[4]. Indeed, in a clinical trial without a no-treatment control arm, psychological factors cannot be disentangled from the natural history of the disease and from regression to the mean.

What we need today in the field of psychiatry is to approach the nocebo effect in the same way as done for other medical conditions, where we have understood some of the underlying mechanisms. The task is not easy, and certainly it represents a challenge for future psychiatric research, but it is worthwhile, considering that the neuroscientific approach to nocebo phenomena is paying dividends in other conditions[1,2].

For example, pain is the condition where nocebo effects have been analyzed in most detail. Many mechanisms are at work in nocebo hyperalgesia, including patient-related factors, the psychosocial context, and neurobiological factors. Recent research has identified many biological underpinnings, such as cholecystokinergic and cyclooxygenase hyperactivity[2]. Likewise, brain imaging techniques, including functional magnetic resonance and positron emission tomography, have documented the involvement of several brain regions, and even the spinal cord, in the nocebo hyperalgesic response[5].

This mechanistic approach to the nocebo phenomenon is important for at least two reasons. First, it demonstrates that nocebo effects are associated with changes in the patient's brain. Second, it suggests that the understanding of these effects may lead to better medical practice and clinical trials: in fact, what we want to do in routine clinical practice is to maximize placebo effects while minimizing nocebo effects, whereas in clinical trials we want to minimize both placebo and nocebo effects.

Nocebo phenomena are also important to better address some issues related to the biopsychosocial model. For example, in a recent study, we investigated the role of negative expectations, so important in nocebo phenomena, in hypoxia headache, in order to understand their relative contribution to the generation of headache pain[6]. We found that biological, psychological and social factors are additive not only in the generation of headache, but also in inducing the biochemical changes related to hypoxia, such as the increased activity of cyclooxygenase. This is a straightforward example of how negative psychological factors may interact with biological factors in the generation of illness.

In the setting of clinical trials, nocebo effects represent an important source of confusion and misinterpretations. For example, the rates of adverse events reported in the placebo arms of clinical trials for three different classes of anti-migraine drugs (non-steroid anti-inflammatory drugs, triptans and anticonvulsants) were very high and, most interestingly, the adverse events in the placebo arms corresponded to those of the anti-migraine medication with which the placebo was compared[7]. The most likely explanation for these effects is that the list of possible adverse events in the informed consent forms generates negative expectations.

Depression shows the same effects. In a comparison of the rates of adverse effects reported in the placebo arms of tricyclic antidepressant and selective serotonin reuptake inhibitor (SSRI) trials, the way in which adverse events were recorded influenced the rate of these effects substantially[8]. A total of 143 placebo-controlled randomized trials and data from 12,742 patients were analyzed. More systematic assessment led to higher rates than less systematic assessment. Far more adverse effects were reported in tricyclic antidepressant compared to SSRI placebo groups, e.g. dry mouth, drowsiness, constipation, sexual problems. In general, the adverse effect profiles were strongly influenced by the expectations of investigators and patients, with the adverse effect pattern of the placebo group closely resembling the adverse effects of the drug group.

A better understanding of nocebo effects in psychiatry could be crucial both in the setting of clinical trials and in routine clinical practice. By controlling patients' negative expectations, we could be able to reduce to some extent poor compliance and dropouts.

For example, the way in which informed consent is formulated should probably be revised in order to pay more attention to sentences that could lead to negative expectations. Likewise, doctor-patient interaction should be aimed at avoiding negative communication. In a study on influenza vaccination, people who were informed of the proportion of individuals who do not develop side effects (positive communication) showed less adverse effects than those who were informed of the proportion of individuals developing side effects (negative communication)[9].

In conclusion, we believe that future psychiatric research should try to better understand nocebo phenomena from different perspectives. The neuroscientific approach could give us information on the biology of nocebo effects in mental disorders, while the methodological perspective could help us design better clinical trials. Overall, both medical practice and doctor-patient relationship could benefit from this.

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Key lessons learned from the INDIGO global network on mental health related stigma and discrimination

Stigmatization of people with mental illness can contribute to adverse consequences, including poor access to mental and physical health care; reduced life expectancy; exclusion from higher education and employment; increased risk of contact with the criminal justice system; victimization; poverty and homelessness[1].

The WPA Open the Doors programme was initiated by one of us (NS) in 1999 and included both action and research components in 23 countries worldwide. This work led to the creation of the WPA Stigma Section, and to establishing a series of biannual international stigma related conferences, entitled Together Against Stigma.

We subsequently created the INDIGO (International Study of Discrimination and Stigma Outcomes) Research Network to undertake research related to stigma and discrimination (http://www.indigo-group.org/). Here we summarize the work of the INDIGO network over the last decade, and set out what we have learned.

In the first phase, colleagues in 27 countries worldwide agreed to join the network, and we realized that no suitable scales existed to measure mental illness related discrimination. We therefore created the Discrimination and Stigma Scale (DISC), which was found to have strong psychometric properties[2]. Since 2012, the DISC-12 scale has been accessed by 216 research users in 55 countries worldwide.

In our first global stigma project, the DISC-12 scale was used to interview 729 people with a clinical diagnosis of schizophrenia across 27 countries. The results showed that over 90% had experienced discrimination because of their mental health status[3]. Most people (72%) reported a need to conceal their diagnosis. The results confirmed the universality of discrimination adversely affecting people with schizophrenia.

We next assessed 1,082 people with major depressive disorder in 35 countries, and found that 79% reported experiencing discrimination in at least one life domain. In exploring the data further, we unexpectedly found higher levels of experienced discrimination in high-income compared with middle- and low-income countries (LMIC)[4].

We conceptualized stigma in relation to its three components of knowledge, attitudes and behaviour. We therefore created and psychometrically tested the following toolkit of scales and measures across those domains, to be freely available to researchers worldwide: the Barriers to Access to Care Scale (BACE), formulated following a systematic review of barriers to help-seeking[5]; the Costs of Discrimination Assessment (CODA), assessing the costs related to mental illness related discrimination[6]; the short version of the DISC-12 (DISCUS) scale, with strong psychometric properties and comparable reliability and validity to the original scale; the Mental Health Knowledge Schedule (MAKS), assessing factual items related to mental health[7]; the Mental Illness: Clinicians' Attitudes (MICA) scales, evaluating attitudes among health care professionals or medical students towards people with mental illness[8]; the Questionnaire of Anticipated Discrimination (QUAD), exploring future expectation of discrimination[9]; and the Reported and Intended Behaviour Scale (RIBS), a short measure of the above domains[10].

These scales have been designed for global and open access use. They can be translated into any language, provided that each translation is copied to the repository at King's College London, to be freely available for other researchers. Up to now, the INDIGO scales have been translated into a total of 31 languages. They have been used in 67 countries during the last five years. The scales are available on request (maria.milenova@kcl.ac.uk).

Following the toolkit phase of work, we more directly focused upon intervention studies. We produced a narrative and a systematic review of the global literature on interventions to reduce stigma and discrimination[1] and a paper on intervention studies in LMICs.

Taken as a whole, these reviews establish that: a) social contact (i.e., interpersonal contact between people with and without experience of mental illness) is the strongest proven active ingredient to reduce mental illness related stigma and discrimination; b) such social contact is most effective in educational settings for young people; c) there is emerging evidence that virtual/social media contact may be as effective as direct face-to-face contact; and d) there is a research gap on all of these issues in LMICs.

Since the INDIGO network was established, we have learned the following lessons on how a network may become successful, productive and sustainable:

- *Clear ground rules* are vital in terms of what are the role and responsibilities of all partners.
- *Establishing a learning collaborative*: we actively encourage sites to support each other, particularly in similar language or resource-level settings.
- *Taking a long-term view for sustainable capacity building*: for an international research network to survive, let alone thrive, it is necessary to purposively support early- and mid-career academic staff**.**
- *A distributed model of leadership for shared responsibilities and co-operation*: we have found it useful to distribute specific roles into discrete work packages, and to establish task teams for each of these tasks.
- *Freedom within a framework*: the coordinating centre agrees with project staff what their ultimate products or deliverables will be, when they will be delivered, and the intermediate steps, or milestones that will have to be completed to a given set of time points.

- *Multidisciplinary approach to research*: the network provides a unique resource for the development of new research in the field of stigma by bringing a variety of inter-disciplinary skills.
- *Regular communication*: it is vital to build a sense of belonging to a valued group of colleagues, and to celebrate intermediate as well as final project successes.

From our work in the INDIGO network so far, we have learned that stigma and discrimination are universal, that they are reversible, and that there are some variations in their manifestations across cultures. We continue to welcome colleagues who wish to join this network, and we are now considering how the learning generated by the network may be used to counteract stigma in other arenas.

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Addressing the opioid crisis globally

Since 2015, the United Nations Office on Drugs and Crime (UNODC) - World Health Organization (WHO) Informal Scientific Network (ISN) has strived to bring the voice of science, as it pertains to addiction medicine, to inform critical discussions at the Commission on Narcotic Drugs (CND), the policy-making body of the United Nations with prime responsibility for drug control matters[1,2].

The opioid overdose crisis represents an increasingly global challenge[3], one associated with high rates of morbidity and mortality[4,5]. The contours of the epidemic have been most extensively documented in North America, but serious situations are developing around the world. Meanwhile, millions of people worldwide suffer moderate to severe pain without access to opioid analgesics, despite the provisions of the international drug conventions[1]. For these reasons, during the CND's 61st session, the ISN examined the opioid overdose crisis and presented a statement with recommendations for consideration of the CND.

Effective public health measures are needed to maintain the delicate balance between reducing barriers to pain treatment and preventing the expansion of the opioid overdose epidemic.

The opioid overdose epidemic is complex, heterogeneous, multifactorial and rapidly changing. Three conditions appear to have contributed to the epidemic of opioid related deaths in North America: the overreliance on, and prescription and use of excessive doses of opioid analgesics for pain management[6], the availability of cheap pure heroin, and the large-scale supply of illicit fentanyl and analogues[7].

Among the key strategies to control the current opioid crisis in America or to prevent such crisis in other countries, it is recognized that access to comprehensive, evidence-based and quality treatment for opioid use disorders in a continuum of care model is essential. Appropriate services should be provided to the people with opioid use disorders in accordance with the stage and severity of the disorders, with responses ranging from low-threshold outreach interventions to multifaceted and multistage rehabilitation and social reintegration programs, including treatment for medical or psychiatric comorbidities.

Funding to implement treatment services at the local level should be monitored and accredited by national authorities to ensure that services provided are the most cost-effective.

Importantly, medications need to be provided free of charge and following clinical guidelines for medication management of opioid use disorders. In addition, the health workforce (doctors, nurses, nurse practitioners, physician assistants) needs to be fully engaged and appropriately trained on the screening, treatment and support of individuals suffering from an opioid use disorder.

The expansion of access to naloxone has proven an effective means of preventing ovedose facilities from opioids. Naloxone should be made available to health care professionals and other first responders, along with the proper training in its administration as well as in other life-saving resuscitation techniques.

Breaking social exclusion and addressing marginalization, stigmatization and discrimination of patients with opioid use disorders are all essential elements to ensure access to public health services, treatment retention and effectiveness of interventions, including overdose prevention. National policies and guidelines should be in place to promote the prevention of substance use, as well as quality treatment and care of substance use disorders. Given the high rate of relapse and overdose deaths following prison release, it is essential to establish tighter coordination between the health and criminal justice system, to ensure effective opioid overdose prevention measures as a part of the substance use disorder treatment and care programs, during and after release.

In addition, countries need to implement systematic data collection, monitoring and evaluation of early warning systems to prevent and develop strategies to reduce abuse and misuse of existing and new emerging synthetic opioids.

The ISN issued the following recommendations:

- Increasing access to quality, evidence-based treatment of substance use disorders in a continuum of care model, taking into consideration the chronic and relapsing nature of addiction and including community-based outreach services, long-term recovery management and coordination of services/institutions/civil society in a systematic response.
- Recognizing access to treatment, including pain management of substance use disorders, as a fundamental right to health, to relieve suffering and protect patients against cruel, inhuman or degrading treatment.
- Providing appropriate pain management to avoid misuse of opioid analgesics and other potentially addictive medicines, whilst recognizing the burden caused by the chronic pain condition.
- Adopting strategies, as developed by UNODC and WHO together with relevant stakeholders, to ensure the rationally regulated, safe, and effective availability of opioids for the treatment of pain, and of medications for the treatment of opioid use disorders (methadone, buprenorphine and naltrexone) and opioid overdose reversal (naloxone) at an affordable price to ensure access to these essential and sometimes life-saving medications. The strategy should also address other barriers to access controlled drugs for medical purposes, such as inadequate legislation and regulation, deficient training of health care providers, and lack of awareness combined with a lingering stigma amongst the public.
- Utilizing standardized, evidence-based screening to assess the risk for opioid misuse amongst those who request pain treatment.
- Providing additional monitoring and accurate supervision, when prescribing opioids to individuals at risk of substance use disorders.
- Providing accessible screening and treatment services for

mental health conditions, particularly among the youth, to prevent the development of vulnerabilities for substance use disorders.
- Facilitating research with controlled substances, including synthetic opioids, to generate new knowledge on how to revert overdoses or mitigate adverse effects. As stated in the UN Conventions, controlled substances should be available for medical and scientific purposes. Unnecessary barriers should be removed.
- Inviting WHO to update the guidelines for treatment of opioid use disorders and start developing new guidelines for the effective management of chronic non-cancer pain.

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Neurocognitive disorders in ICD-11: a new proposal and its outcome

The appropriate classification of diseases involving neurocognitive impairment has been an area of professional dissent between psychiatry and neurology for the past several years. This has been reflected in the groupings of "neurocognitive disorders" in chapter 6 on mental disorders and "disorders with neurocognitive impairment as a major feature" in chapter 8 on diseases of the nervous system in the draft version of the ICD-11.

The disagreement about the placement of dementias in ICD-11 has been settled by international consensus after the intervention of several scientific associations in the mental health field[1], with the dementia categories being included in chapter 6 and their underlying causes being represented in chapter 8, following the logic of ICD-10.

In August 2018, a group of neurologists posted on the ICD-11 website a "complex hierarchical changes proposal" to replace "vascular dementia" with "vascular cognitive impairment" (VCI)[2]. Referring to the publication of a "primer"[3], VCI was defined as "the contribution of vascular pathology to any severity of cognitive impairment, ranging from subjective cognitive decline and mild cognitive impairment to dementia". In essence, the proposal argued that the term "vascular dementia" in chapter 6 had become "obsolete" and should be replaced by VCI in chapter 8.

The stated rationale[3] was that "vascular pathology is common in the elderly with and without cognitive decline... mostly caused by a mixture of degenerative brain pathology in association with ischemia...; this requires detailed neurological and imaging workup and will forever preclude the diagnosis of 'vascular dementia' without proper investigations". The proposal concluded: "We also suggest to our colleagues dealing with the mental health chapter 6 to reconsider their definition of vascular dementia. It is crucial that ICD-11 truly reflects modern 21st century thinking and practice".

After consultation with the World Health Organization (WHO), a roundtable discussion with invited psychiatric experts was organized at the World Congress of Psychiatry in Mexico City in September 2018. A consensus was reached to post a critical commentary after endorsement by a larger group of experts representing a variety of national and international scientific psychiatric associations[4].

The commentary, posted on October 19, 2018, stated that:

- Even if it would be appropriate to include "cognitive impairment" as a clinical manifestation of diseases or disorders, its proper location would be under "neurocognitive disorders" in chapter 6. Moreover, it remains unclear why "vascular" should be attached to cognitive impairment, since the authors rightly claim that the vascular one is almost never the exclusive aetiology of that impairment.
- Additionally, the VCI proposal refers to a patho-clinical continuum of cognitive impairment adopted from current Alzheimer research models[5]. It lacks a clear classificatory concept, a convincing definition, an explicit operationalization of the "cognitive" profile, as well as a valid severity grading of "impairment". Hence, its diagnostic and classificatory relationship with subjective (preclinical), mild or se-

vere forms (dementia) remains unclear and not consistently developed for application in ICD-11.
- Concerning the predominantly vascular forms of neurocognitive disorders, neither the close similarity of the terms "vascular cognitive impairment" and "vascular dementia" nor the latter's existing option for post-coordination with the detailed category of "cerebrovascular diseases" in chapter 8 are reflected in the proposal. Hence, the proposal to relocate, rename or replace vascular dementia by VCI is neither consistent with current classification principles[6] nor ready for implementation.
- Accordingly, using the term VCI and proposing pure vascular cognitive "impairment" as a separate category is not convincing. Moreover, "vascular" as a collective term refers to very different cerebrovascular diseases, which may interact with other aetiologies, and whose role may change over lifetime. Therefore, "vascular" should not be used as a fixed combination in a broad-spectrum term like VCI, spanning several diagnostic stages and aetiologies of cognitive impairment.

Given the scientific state of the art[3,5], the classificatory rules of ICD-11[6], and the existing ICD-11 classification and coding of neurocognitive disorders across chapters 6 and 8[1], the following modifications were proposed:

- For "vascular dementia", a coding note says that "this category should never be used in primary tabulation". By post-coordination, "6D81 Vascular dementia" optionally could already be "associated with" various "cerebrovascular diseases" from chapter 8, with "6D86 Behavioural or psychological disturbances in dementia", and with an additional severity code. "6D80.2 Alzheimer disease dementia, mixed type, with cerebrovascular disease" already provides an opportunity to code mixed etiological forms of dementia as suggested in the above proposal. In case of multiple aetiologies, all that applies could be coded.
- For classificatory consistency, however, vascular dementia should be reformulated as "dementia due to cerebrovascular disease" following the pre-coordinated formulation ("dementia due to...") of other dementia categories in chapter 6 and should mandatorily be post-coordinated with the respective category of cerebrovascular diseases in chapter 8.
- A related issue is the aetiological underpinning of "6D71 Mild neurocognitive disorder". Post-coordination offers an opportunity to add as causing conditions a number of "diseases classified elsewhere", from chapter 8 and others. However, the option for also adding "cerebrovascular diseases" or multiple conditions is missing. This should be corrected.
- Together with these proposed modifications, the current ICD-11 version of vascular related neurocognitive disorders would already allow coding for the mild and severe stages of vascular or mixed neurocognitive disorders.

In conclusion, the implementation of a new category of VCI in chapter 8 seems premature and not acceptable from the perspective of: a) the underdeveloped status of the classificatory concept of this entity, and b) its lack of adaptation to the present structure and coding options of ICD-11 neurocognitive disorders.

On October 20/21, 2018, the authors of the VCI proposal posted an agreement[7] with the above proposals and renounced the introduction of VCI in chapter 8. After being conveyed to responsible WHO bodies, the debate's outcome and resulting actions were officially endorsed at the WHO Family of International Classifications ICD-11 conference in Seoul.

Since December 18, 2018, the proposed changes are implemented both in the frozen and the maintenance version of ICD-11 (https://icd.who.int/browse11/l-m/en).

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Public stakeholders' comments on ICD-11 chapters related to mental and sexual health

A unique strength of the development of the World Health Organization (WHO)'s ICD-11 classification of mental, behavioural and neurodevelopmental disorders has been the active input from multiple global stakeholders.

Draft versions of the ICD-11 for Morbidity and Mortality Statistics (MMS), including brief definitions, have been available on the ICD-11 beta platform (https://icd.who.int/dev11/l-m/en) for public review and comment for the past several years[1]. Submissions were reviewed by the WHO for the development of both the MMS version of the ICD-11 and the version for clinical use by mental health specialists, the Clinical Descriptions and Diagnostic Guidelines (CDDG)[1]. Here, we summarize common

themes of the submissions for the categories that generated the greatest response.

All comments and proposals were reviewed for categories currently classified in the chapter on mental and behavioural disorders in ICD-10, although some of these have been reconceptualized and moved to new ICD-11 chapters on sleep-wake disorders and conditions related to sexual health[2].

Between January 1, 2012 and December 31, 2017, 402 comments and 162 proposals were submitted on mental, behavioural and neurodevelopmental disorders, sleep-wake disorders, and conditions related to sexual health. The largest number of submissions related to mental, behavioural and neurodevelopmental disorders focused on compulsive sexual behaviour disorder (N=47), complex post-traumatic stress disorder (N=26), bodily distress disorder (N=23), autism spectrum disorder (N=17), and gaming disorder (N=11). Submissions on conditions related to sexual health mainly addressed gender incongruence of adolescence and adulthood (N=151) and gender incongruence of childhood (N=39). Few submissions were related to sleep-wake disorders (N=18).

We performed qualitative content analysis to identify the main themes of submissions related to categories on which there were at least 15 comments. Thus, 59% of all comments and 29% of all proposals were coded. Submissions were independently rated by two assessors. Multiple content codes could apply to each submission. Inter-rater reliability was calculated using Cohen's kappa; only codings with good inter-rater reliability ($\kappa \geq 0.6$) are considered here (82.5%).

Compulsive sexual behaviour disorder received the highest number of submissions of all mental disorders (N=47), but often from the same individuals (N=14). The introduction of this diagnostic category has been passionately debated[3] and comments on the ICD-11 definition recapitulated ongoing polarization in the field. Submissions included antagonistic comments among commenters, such as accusations of a conflict of interest or incompetence (48%; κ=0.78) or claims that certain organizations or people would profit from inclusion or exclusion in ICD-11 (43%; κ=0.82). One group expressed support (20%; κ=0.66) and considered that there is sufficient evidence (20%; κ=0.76) for inclusion, whereas the other strongly opposed inclusion (28%; κ=0.69), stressing poor conceptualization (33%; κ=0.61), insufficient evidence (28%; κ=0.62), and detrimental outcomes (22%; κ=0.86). Both groups cited neuroscientific evidence (35%; κ=0.74) to support their arguments. Few commenters proposed actual changes to the definition (4%; κ=1). Instead, both sides discussed nosological questions such as conceptualization of the condition as impulsivity, compulsivity, behavioural addiction or expression of normal behavior (65%; κ=0.62). The WHO believes that the inclusion of this new category is important for a legitimate clinical population to receive services[4]. Concerns about overpathologizing are addressed in the CDDG, but this guidance does not appear in the brief definitions available to beta platform commenters.

A number of submissions related to complex post-traumatic stress disorder supported its inclusion in ICD-11 (16%; κ=0.62), with none explicitly arguing against inclusion (κ=1). However, several submissions suggested changes to the definition (36%; κ=1), submitted critical comments (24%; κ=0.60) (e.g., concerning the conceptualization), or discussed the diagnostic label (20%; κ=1). Several comments (20%; κ=0.71) emphasized that recognition of this condition as a mental disorder would stimulate research and facilitate diagnosis and treatment.

A majority of submissions regarding bodily distress disorder were critical, but were often made by the same individuals (N=8). Criticism mainly focused on conceptualization (48%; κ=0.64) and the disorder name (43%; κ=0.91). Use of a diagnostic term that is closely associated with the differently conceptualized bodily distress syndrome[5] was seen as problematic. One criticism was that the definition relies too heavily on the subjective clinical decision that patients' attention directed towards bodily symptoms is "excessive". A number of comments (17%; κ=0.62) expressed concern that this would lead to patients being classified as mentally disordered and preclude them from receiving appropriate biologically-oriented care. Some contributors submitted proposals for changes to the definition (30%; κ=0.89). Others opposed inclusion of the disorder altogether (26%; κ=0.88), while no submission (κ=1) expressed support for inclusion. The WHO decided to retain bodily distress disorder as a diagnostic category[6] and addressed concerns by requiring in the CDDG the presence of additional features, such as significant functional impairment.

Submissions concerning conditions related to sexual health showed strong support for removal of sexual dysfunctions and gender diagnoses from the mental disorders chapter and creation of a separate chapter (35%; κ=0.88)[7]. Many submissions (25%; κ=0.97) used a template message provided by the World Association for Sexual Health. Several submissions argued that retaining gender incongruence in the disease classification would harm and stigmatize transgender people (14%; κ=0.80), proposed a different phrasing of the definition (18%; κ=0.71) or a different diagnostic label (23%; κ=0.62). The WHO changed the definitions in part based on the comments received[7].

Interestingly, a large group of submissions on the proposed ICD-11 definition for gender incongruence of childhood expressed opposition to current standards of care by explicitly objecting to social transition and gender-affirming treatment of minors (46%; κ=0.72), matters that, although important and controversial, have to do with treatment rather than with classification. The proposed definition was criticized or opposed in 31% of submissions (κ=0.62), with some using a template provided by the World Association for Sexual Health to urge a revision based on consultation from the community (15%; κ=0.93). Others opposed the diagnosis expressing fear of pathologizing childhood gender diversity (15%; κ=0.93) and claiming that it is unnecessary because there would be neither distress (11%; κ=0.80) nor need for gender-affirming health care (28%; κ=0.65) in children. Some also argued that a diagnosis is not necessary for research purposes, pointing out that research on homosexuality has flourished since its removal from the ICD (9%; κ=0.745). While acknowledging the controversies surrounding

treatment, the WHO retained the category to help ensure access to appropriate clinical care while addressing stigma through its placement in the new chapter of conditions related to sexual health as well as through additional information in the CDDG[7].

In interpreting these comments, it is clear that many of the submissions have been made from an advocacy perspective, often focused on a particular category. It is appropriate for scientific experts to review their recommendations in the light of patient experience and feedback. The WHO has used the comments and proposals on the beta platform in combination with other sources of information, particularly developmental field studies[8,9], as a basis for making modifications in the MMS and CDDG.

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The controversy about cognitive behavioural therapy for schizophrenia

The effectiveness of cognitive behavioural therapy (CBT) in schizophrenia is currently disputed. For example, the UK National Institute for Health and Care Excellence (NICE)[1] recommends this therapy, whereas another influential UK organization, the Cochrane Collaboration, has argued since 2012 that there is no clear evidence that it is effective[2-4].

Of clear relevance here is a network meta-analysis of psychological interventions in schizophrenia published in this journal[5] which found pooled evidence that CBT is effective against positive symptoms. On the contrary, a 2014 meta-analysis by Jauhar et al[6] failed to find clear evidence of effectiveness against this class of symptoms. Since it is important to understand what factors give rise to different results in meta-analyses[7], we, as the authors of those two meta-analyses, decided to examine why such a discrepancy might have arisen.

Bighelli et al[5]'s examination of CBT for positive symptoms was based on 27 trials out of a total dataset of 40 that met their inclusion criteria (the remaining studies contained data relevant to one or more of the other outcomes they examined, e.g., overall symptoms, negative symptoms, relapse/rehospitalization, depression, quality of life, functioning and mortality). In these 27 studies, the pooled effect size was at the upper end of the small range, against both treatment as usual (–0.30; 95% CI: –0.45 to –0.14, 18 trials) and inactive control interventions (–0.29; 95% CI: –0.55 to –0.03, 7 trials). A larger effect size was found for CBT compared to supportive therapy (–0.47; 95% CI: –0.91 to –0.03, two trials). Leaving aside the findings for supportive therapy, where the number of trials was small, these findings in themselves are not greatly different from the overall effect size that Jauhar et al[6] found for positive symptoms against all controls (–0.25; 95% CI: –0.37 to –0.13, 33 trials).

Where the two meta-analyses diverged, however, was in relation to the findings in blind trials. Bighelli et al[5] continued to find a significant effect against treatment as usual (–0.27; 95% CI: –0.41 to –0.13) in 15 blind trials, but not against inactive control (–0.14; 95% CI: –0.37 to 0.09), although the number of studies here was smaller (n=5). In contrast, Jauhar et al[6] found that the pooled effect size for positive symptoms against all controls dropped to very low levels in their sub-analysis of 20 blind trials (–0.08; 95% CI: –0.18 to 0.03).

The divergent findings in blind studies did not reflect differences in the way in which criteria for blindness were applied to the trials included in the two meta-analyses. The approach used was similar, and cross-checking revealed that discrepancies about whether individual studies were rated as "blind", "non-blind" or "unclear" were trivial.

The most important difference between the two meta-analyses was found to concern the inclusion criteria used. While Jauhar et al[6] employed a broad strategy similar to those used by NICE[1] and the Cochrane Collaboration[2-4], the focus in Bighelli et al[5]'s meta-analysis was planned from the outset[8] to be on the efficacy of psychological interventions for treating positive symptoms (the indication CBT was initially developed for). Consequently, trials carried out in patients with predominantly negative symptoms and those enrolling stable patients (i.e., relapse prevention studies) were excluded. Bighelli et al[8] also decided to exclude studies that were carried out in first-episode patients; this was on the grounds that such studies have been found to have significantly higher treatment response rates compared with those in chronic patients.

This methodological difference turned out to be consequential. Although the number of studies of CBT included were not greatly different in the two meta-analyses (27 vs. 33), only 14 of the studies in Bighelli et al[5] were also included by Jauhar et al[6]. This means that Bighelli et al[5] had more studies with positive symptoms as explicit inclusion criteria (14 in Jauhar et al[6] vs.

27 in Bighelli et al[5]).

We therefore conclude that the discrepancy concerning the effectiveness of CBT on positive symptoms of schizophrenia (especially in blind studies) found in our two meta-analyses reflects the substantially differing data sets examined. To reduce confusion in this area, where the study designs are much more variable than those about pharmacological treatments for schizophrenia, we propose that future systematic reviews on psychotherapies for schizophrenia should always document their methods and in particular inclusion criteria in an *a priori* published protocol.

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ICD-11 PTSD and complex PTSD: structural validation using network analysis

The newly released ICD-11 includes two related diagnoses within the section on Disorders Specifically Associated with Stress: post-traumatic stress disorder (PTSD) and complex PTSD (CPTSD)[1].

PTSD has been substantially refined relative to earlier ICD and DSM descriptions. Two symptoms each reflect the three "subdomains" of: a) re-experiencing the event in the here and now, b) avoidance of traumatic reminders, and c) a sense of current threat. The diagnosis now requires the endorsement of one symptom from each of these subdomains, plus evidence of functional impairment.

CPTSD includes the above-mentioned core PTSD symptoms plus three additional subdomains, each comprised of two symptoms, collectively referred to as "disturbances in self-organization" (DSO). These three subdomains are: a) affective dysregulation, b) negative self-concept, and c) disturbances in relationships. The diagnosis of CPTSD requires that the PTSD criteria be met, plus endorsement of one symptom in each of the DSO subdomains, and evidence of functional impairment associated with these latter symptoms. Importantly, a person may only qualify for a diagnosis of PTSD or CPTSD but not both.

Although initial psychometric work has supported the structure of the 12-indicator description of PTSD-CPTSD[2], this model has yet to be empirically validated using diverse methodologies and samples. We used a novel and sophisticated network psychometric approach to examine the structure of this description of PTSD/CPTSD in two large, trauma-exposed samples.

The network approach conceptualizes psychopathology as a complex network of locally associated symptoms[3]. Under this interpretation, the effects of causal factors (e.g., a traumatic event) are proposed to spread throughout the network via direct, symptom-level interactions and reinforcement, and what we might consider to be psychiatric "disorders" are captured in densely connected groups/clusters of symptoms. By focussing on the direct associations between symptoms, the network approach may provide a more detailed and nuanced description of the structure of psychopathology, and help us ascertain how and where our diagnostic constructs overlap.

We analyzed two trauma-exposed samples: a representative sample from Israel[4] (N=1,003; 51.7% female; mean age 40.6±14.5 years), and a sample consisting of internally displaced persons from Ukraine[5] (N=1,790; 67% female; mean age 43.0±15.8 years). Symptoms of PTSD and CPTSD were self-reported using the recently developed International Trauma Questionnaire[2], a 12-item measure designed to reflect the ICD-11 descriptors of PTSD/CPTSD.

Regularized partial correlation networks were estimated separately for both samples using the R package qgraph[6]. In order to determine whether symptoms clustered in a manner reflecting the new ICD-11 criteria for PTSD-CPTSD, exploratory graph analysis (EGA) was performed using the EGA package[7]. EGA uses the walktrap algorithm[8] to identify clusters of highly associated symptoms within networks, and recent simulation work has demonstrated that it outperforms traditional methods for uncovering the underlying structure of data (e.g., Horn's parallel analysis, Kaiser-Guttman rule), particularly when the correlations between the underlying dimensions are high, and the number of indicators per dimension is low[7]. The networks were then compared across samples using the NetworkComparisonTest package[9], which tests for invariance in structure and connectivity using a permutation test procedure. Finally, to quantify and compare the overall importance/influence of individual symptoms across the two groups, three common measures of centrality were calculated: strength, betweenness and closeness.

The ICD-11 model of PTSD-CPTSD was supported in both samples. EGA identified two clusters corresponding to PTSD and DSO, and this solution was confirmed when the networks were re-estimated using 1,000 bootstrapped draws (for network graphs, see https://www.traumameasuresglobal.com/network-analysis-paper). The five strongest item-level associations mirrored five of the six diagnostic subdomains of PTSD and CPTSD: re-experiencing, avoidance of traumatic reminders, sense of threat, negative self-concept, and disturbances in relationships. Symptoms of affective dysregulation (hypoactivation and hyperactivation) were not highly associated with one another.

The two networks did not differ significantly in terms of overall connectivity (p=0.06). Structural invariance was not supported (p<0.001); however, post-hoc permutation tests revealed that this was due to a significant difference in only one item pair: the two avoidance items were more strongly associated in the Israeli sample. All other item-level associations were not statistically different across the two samples, and thus the network structure was judged to be broadly consistent across the two groups. The centrality indices were also broadly similar across the two groups; however, "avoidance of external reminders" was notably higher in strength in the Israeli sample.

In summary, this is the first network psychometric study of the newly developed ICD-11 diagnostic criteria for PTSD and CPTSD. Across two trauma-exposed samples, the structural validity of these disorders was supported; symptoms formed two broad clusters corresponding to PTSD and DSO, and the strongest associations within these clusters were between symptoms from the established PTSD and DSO subdomains.

However, items measuring hypoactivation and hyperactivation were more strongly associated with other symptoms than with each other, which questions the idea of affective dysregulation as a unitary subdomain of CPTSD. Furthermore, despite consistency in overall network structure, differences in strength centrality were observed across the two samples.

Future research could explore whether such differences can be attributed to sample/trauma characteristics (e.g., type of trauma, length of time since trauma, demographic factors). The identification of symptoms that take on context-specific relevance may be a focal point for targeted interventions.

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Sluggish cognitive tempo: the need for global inquiry

The construct of "sluggish cognitive tempo" (SCT), a set of symptoms characterized by excessive daydreaming, mental confusion and fogginess, drowsiness, and slowed thinking and behavior, was introduced over three decades ago.

Despite a recent increase in research attention, SCT remains largely unfamiliar to researchers and clinicians alike. Moreover, SCT has been primarily examined in the US, with only a handful of studies from Western Europe and even fewer from other parts of the world.

Here I provide a brief summary of key SCT findings and draw attention to the need for greater worldwide investigation of this construct, including its phenomenology, etiology and course, concomitants and developmental consequences, and clinical implications.

The study of SCT has been closely tied to that of attention-deficit/hyperactivity disorder (ADHD), and this historical association remains present in much of the literature. SCT is strongly associated with ADHD inattentive symptoms, though meta-analytic findings also support their differentiation[1].

Another consistent finding is the separation of SCT and ADHD inattention in their relations with other psychopathologies: SCT is strongly associated with internalizing symptoms, especially depressive symptoms, yet unassociated or negatively associated with externalizing behaviors when controlling for ADHD inattention; conversely, ADHD inattention is consistently associated with externalizing behaviors and less clearly associated with internalizing symptoms when controlling for SCT[1,2].

Consistent with SCT's association with internalizing symptoms, there is emerging evidence of an association between SCT and suicide risk[3], and SCT symptoms are also associated with social difficulties, particularly social withdrawal and isolation[1,2]. Findings for academic functioning and neurocognition are somewhat mixed, though there is initial evidence for SCT being associated with greater academic impairment, lower academic achievement scores, slower processing speed, and poorer sustained attention[1,2].

Finally, SCT predicts non-response or poorer response to methylphenidate among children with ADHD[4], underscoring

the clinical relevance of this constellation of symptoms. Still, the study of SCT remains in its infancy, with a number of findings yet to be replicated and other areas of inquiry untouched entirely.

This is an opportune time for a worldwide study of SCT. A recent meta-analysis identified SCT symptoms that are empirically distinguishable from ADHD inattentive symptoms[1], and subsequent measurement work has validated SCT rating scales, with a consistent symptom set that can be used across parent, teacher, child and adult informants.

Several translations of these measures are starting to emerge or are currently in progress. It has become clear that the wording of some SCT items may be culture-bound idioms in the English language that are not readily subject to translation (e.g., "mind gets mixed up", "seems to be in a fog"). A standard symptom set that can be readily translated into various languages is an important first step to the global inquiry of SCT.

As validated measures become available, they can be used to examine whether SCT symptoms are similarly identifiable across and within cultures. This is necessary to establish the transcultural validity of SCT and better understand its phenomenology, development, and functional impact. It is possible that SCT is more prevalent or harmful in certain contexts. For example, SCT-related shyness and withdrawal may be more detrimental for broader social functioning in some cultural contexts compared to others[5].

At the same time, it should be considered whether the presence of SCT and its impact on functional outcomes is attributable to, or exacerbated by, societal factors, in ways that echo findings linking variation in ADHD diagnosis rates to educational accountability policies in the US[6]. The worldwide study of SCT would also allow for investigations of global factors such as solar intensity that have been associated with variation in ADHD prevalence rates[7].

There may also be different cultural attributions for SCT behaviors (e.g., daydreaming), that could in turn have important implications for what prevention and intervention efforts would be perceived as acceptable. These types of intriguing questions can only be addressed if SCT arises to a level of global inquiry.

Finally, it has already been suggested that SCT may be a new psychiatric condition identified, in part, to provide more opportunities for psychotropic intervention[8]. Establishing the global prevalence and impact of SCT would help alleviate concerns that the SCT construct is garnering empirical validation not for the clinical needs of patients but for the profits of pharmaceutical companies.

It took over 40 years before a seminal review published in this journal asked whether ADHD was an American condition[9]. It would be prudent to learn from the history of ADHD and to examine the culture-bound or global nature of SCT sooner rather than later.

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WPA Secretariat: keeping pace with changing times!

The WPA Secretariat is established to facilitate the functioning of the Association in achieving its aims and objectives. It is constantly on the move, keeping pace with changing times and consistent with the requirements of WPA Member Societies. Its registered office is in Geneva, Switzerland and is currently located at the Department of Psychiatry, Geneva University Psychiatric Hospital.

The WPA Secretary General has the governance responsibility to ensure that the Secretariat supports the Executive Committee in carrying out all the administrative tasks required for the work of the Association[1]. This includes the dissemination of reports, minutes and other materials to all WPA components.

As a testimony of change, a new edition (5th) of the WPA Manual of Procedures has been adopted and published in June 2018. As always, it complements the WPA Statutes and By-Laws by describing the procedures for the conduct of all activities of the Association consistent with its constitutional mandate. The increased complexity of the work of the WPA and its global outreach makes it necessary to have a Manual of Procedures which is easily available online to all WPA components. This new edition incorporates the amendments to the Statutes and By-Laws approved by the General Assembly held in Berlin in October 2017.

A Chief Executive Officer has been appointed since 2016 who manages the WPA Secretariat on a day-to-day basis. She reports to the President and the Secretary General and receives guidance from the Executive Committee. She submits proposals concerning the employment of staff, having consulted with the Secretary for Finances regarding budgetary implications. She selects the staff in consultation with the President and Secretary General, ensuring that they have integrity and the relevant skills according to their specific job descriptions. In consultation with the Secretary General, she ensures that the WPA employees are managed according to local employment legislation and procedures. The Secretary General is responsible for staff complaints and ensures that there is a grievance and appeal procedure, approved by the Executive Committee.

The Secretariat organizes and maintains the WPA archive, including both electronic and paper components. All substantial correspondence (i.e., correspondence relevant to the WPA structure and functioning) and documentation received or issued by any WPA component should be kept in the Secretariat. We have an Archives Room at the WPA Secretariat. Plans are afoot to organize this area more effectively and for electronic archiving of all essential documents stored there. Members of the Executive Committee may request access to any internal document. Members of the Council, Zonal Representatives, Scientific Section officers and Presidents of Member Societies may request copies of documents relevant to their functions. Routine requests will be dealt with by the Chief Executive Officer, who will consult with the Secretary General on more complex requests as necessary.

The Secretariat staff develops and continually updates information on postal addresses, telephone numbers and e-mail addresses for all components of the Association and their officers, and provides an electronic directory of WPA components upon request to all individuals listed in that directory.

WPA News used to be prepared every three months and distributed electronically. Now we are planning to have an E-WPA Newsletter every two months. The Newsletter will present recent information on key activities of the Association and on international developments in the field of mental health. Members of the Executive Committee and other WPA components may submit contributions for the Newsletter. The final version is reviewed and edited by the Secretary General in consultation with the President and the Executive Committee.

Internal documents are available from the WPA Cloud at https:\\share.wpanet.org for the WPA components. WPA Cloud access is password protected.

The WPA website (www.wpanet.org) aims to facilitate the wide international exchange of WPA and professional information relating to educational initiatives, Scientific Sections, publications, meetings and other WPA activities[2,3]. It can also offer, if the Executive Committee decides that a specific need exists, selected educational information on psychiatry, mental health and related sciences to the general public. Public documents appear on the website: these include the Association's Action Plan[4,5]; application procedures and forms for Member Societies, Affiliated Associations and Individual Members; WPA News (including back issues); Guidelines Concerning Support from External Sources for WPA Activities; WPA Meetings Policy; Consensus Statements[6,7] and Curricula[8], and Ethical Statements including the Madrid Declaration. These are available for distribution in paper or electronic forms as appropriate. We are now planning to launch a new "state of the art" website shortly.

The WPA Executive Committee has just approved a WPA system of staff appraisals, the format of the appraisal forms, and a document on risk management and business continuity. Undoubtedly, it is good practice in an organization such as the WPA to identify and then review any potential risks faced and to consider how these risks might be mitigated. Similarly, putting in place a business continuity plan is a progressive step.

Thus, changes are taking place at the WPA Secretariat which will definitely enhance the image and the objectives of the WPA, making our Member Societies closer to the organization.

Roy Abraham Kallivayalil
WPA Secretary General

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HIV/AIDS psychiatry – a paradigm for HIV prevention and integrated compassionate care

The WPA Section on HIV/AIDS Psychiatry defines its field as the subspecialty of consultation-liaison psychiatry that focuses on prevention, care and treatment of HIV and AIDS; psychiatric aspects of risk behaviors and their antecedents; psychiatric manifestations of HIV and its stigma; psychological consequences of HIV infection and its multimorbidities, and their impact on persons infected with and affected by HIV; and the imperative for an integrated biopsychosocioculturral approach to prevention, care and adherence[1].

In 1981 AIDS was a novel, severe, complex and devastating fatal systemic illness of unknown cause characterized by immune suppression, multimorbid opportunistic infections and cancers, and psychiatric disorders including dementia. Our contemporary definition takes into account the remarkable strides that have transformed AIDS into a preventable and manageable chronic illness for persons with access to HIV medical care and treatment with antiretrovirals. However, if HIV medical care is unavailable and/or psychiatric illness impedes access to diagnosis and treatment, persons with HIV are vulnerable to unnecessary and avoidable suffering and progression of illness, as was common in the early stages of the HIV epidemic.

Despite progress in HIV prevention, diagnosis and treatment, 36.9 million people are living with HIV worldwide and 1.8 million become infected with HIV each year[2]. Of 36.9 million persons living with HIV, an estimated 9.4 million are unaware that they are infected and can unknowingly transmit the virus to others[2].

As the HIV pandemic ends its fourth decade, psychiatrists and allied mental health professionals can play a role in both prevention of HIV and compassionate care of persons infected with HIV and its stigma. HIV/AIDS is a highly stigmatized preventable illness caused by a virus and most commonly transmitted through risky human behaviors. The HIV pandemic is catalyzed and maintained by psychiatric disorders which can be vectors of HIV transmission and barriers to treatment adherence.

HIV prevention and care are relevant at many points throughout the life cycle. Psychiatric treatment has a significant impact on morbidity and mortality and special implications for public health and general medical and mental health care[1]. Psychiatrists are in a unique position to mitigate HIV risk behaviors, minimize risk of HIV transmission, and provide education and psychiatric care to improve HIV diagnosis and treatment.

All psychiatrists in clinical practice can play a direct role in HIV prevention by including HIV testing as part of routine evaluation of every patient. Through encouraging routine HIV testing, psychiatrists can improve diagnosis in persons living with HIV and begin to normalize HIV testing. Awareness of HIV status through routine testing can lead to early initiation of antiretroviral therapy and thus reduce morbidity, suffering and mortality as well as HIV transmission.

People living with HIV who adhere to antiretroviral therapy and have achieved viral suppression with an undetectable viral load cannot transmit HIV sexually. This is the premise behind the Undetectable equals Untransmittable (U=U) initiative. The U=U message embodies the concept of treatment as prevention and enables persons with sustained viral suppression to live without fear of transmitting HIV. The knowledge that U=U can help reduce fear and stigma associated with HIV[3].

Psychiatrists routinely take psychosocial, trauma, substance use and sexual histories and evaluate for psychiatric disorders, and can refer HIV negative persons who are at substantial risk of infection for evaluation for pre-exposure prophylaxis (PrEP)[4,5]. PrEP was approved by the US Food and Drug Administration in 2012 to prevent the transmission of HIV. It is comprised of a two-drug antiretroviral regimen (emtricitabine and tenofovir disoproxil fumarate, TDF) that is available in a single tablet[5]. Its use is recommended for HIV negative persons at substantial risk of HIV acquisition, including men who have sex with men and intravenous drug users. PrEP must be taken on an ongoing basis while the HIV negative person remains at substantial risk.

While the evidence for prevention with the use of PrEP is strong, its efficacy is highly dependent on consistent use[4,5]. Psychiatrists have a crucial role in assessing for barriers to adherence as well as identifying potential risk compensation. Generally, PrEP is well tolerated, but TDF may cause nephrotoxicity and bone loss[4].

Crisis intervention and emergency psychiatry are areas in which post-exposure prophylaxis (PEP) for HIV negative persons accidentally exposed to HIV during a sexual encounter or injection drug use can take place. Accidental exposure to HIV is a medical emergency. Referral or treatment with a three-drug regimen (tenofovir, emtricitabine, and raltegravir or dolutegravir) for 28 days can prevent infection as long as it is started within 72 hours after exposure[6].

The WPA Section on HIV/AIDS Psychiatry was developed from an Academy of Consultation-Liaison Psychiatry Special Interest Group that was founded in 2003. It was designated a Section of the WPA in 2012 and has grown from 32 members in 2003 to 459 in 2019. Members have defined our subspecialty, given numerous presentations, contributed articles and chapters, and edited or written three textbooks[7-9] on HIV/AIDS psychiatry. They have presented at WPA meetings throughout the world and have collaborated in presentations with other WPA Sections. As a result of the biopsychosocial complexities of HIV/AIDS psychiatry, there is potential for intersectional collaborative work with WPA Sections on Addiction Psychiatry; Old Age Psychiatry; Perinatal Psychiatry and Infant Mental Health; Psychiatry and Human Sexuality; Psychiatry, Medicine and Primary Care; Psychotherapy; Public Policy and Psychiatry; Stigma and Mental Illness; Suicidology; Transcul-

tural Psychiatry; Urban Mental Health; and Women's Mental Health.

HIV/AIDS psychiatry provides a paradigm for consultation-liaison psychiatry and integrated compassionate care. Our Section members are dedicated to academic, clinical, research and administrative aspects of HIV and AIDS. They use consensus surveys to inform research on best practices of HIV psychiatric care and have published work on use of psychotropic medications. They explore ways to improve doctor-patient communication skills and diminish stigma in the care of persons with HIV and AIDS.

HIV/AIDS psychiatry has broadened the depth and scope of consultation-liaison psychiatry to include prevention, public health, and global psychiatry[1].

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Current goals of neuroimaging for mental disorders: a report by the WPA Section on Neuroimaging in Psychiatry

The WPA Section on Neuroimaging in Psychiatry was established in 1996 in Madrid, during the 10th World Congress of Psychiatry. The main goals of the Section include the dissemination of innovative methodological approaches as well as research findings from different applications of neuroimaging techniques in psychiatry; the sound integration of clinical and neuroimaging research; and the promotion of collaborations with other WPA Scientific Sections and among researchers interested in the field across the world.

In line with these goals, the Section organized, throughout the years, symposia in World Congresses of Psychiatry and International WPA Meetings, and promoted joint initiatives with other WPA Scientific Sections (e.g., with the WPA Schizophrenia Section during the WPA International Congress in Prague in 2012, and with the WPA Psychophysiology Section during the World Congress of Psychiatry in Madrid in 2014).

In 2015, the Section officers (S. Galderisi, L. DeLisi and S. Borgwardt) discussed the opportunity to review decades of research on neuroimaging in schizophrenia and primary psychotic disorders, in the light of many findings suggesting that abnormalities of brain structure and function are associated with psychiatric disorders but do not reflect boundaries of current diagnostic categories.

They envisaged the need to acknowledge that neuroimaging research, up to now, failed to meet the expectations of scientists and clinicians looking for the discovery of biomarkers of current diagnostic categories, but opened important perspectives for future routine applications in the field of early identification of mental disorders and response to treatment.

These considerations gave rise to the plan of producing a book on neuroimaging in psychiatry. In the light of the huge bulk of research in the field, the officers decided to start from psychoses, and elaborated the outline of what we hope is just the first of a series of books, i.e., *Neuroimaging of Schizophrenia and Other Primary Psychotic Disorders*[1]. Several outstanding scientists agreed to collaborate to the project, and the book is now available in both paper and electronic versions.

The volume reviews structural, functional, neurochemical and multimodal neuroimaging studies, within a transnosographic perspective of primary psychotic disorders, and provides an in-depth coverage of current achievements and limitations of neuroimaging research in these disorders. Throughout the book, the authors emphasize that no specific neuroimaging abnormality can be considered as a biomarker for any diagnostic category so far; nevertheless, several documented abnormalities are relevant to important clinical features, such as the severity of the clinical picture, the progression and persistence of symptoms over time, and the response to treatment.

The book highlights current goals of neuroimaging research in psychoses: translating neuroimaging findings into clinical practice, in order to add value to the existing clinical assessment; moving from differences at the group level to the individual level; and identifying quantitative indices supporting clinical decisions. Promising results in this field come from machine learning, i.e., the implementation of algorithms able to learn from the experience and attribute specific characteristics to various samples, by integrating different variables, such as clinical, neurocognitive, neuroimaging and genetic data. In the near future, this progress may contribute to improve the predictive accuracy of diagnosis and prognosis[2].

The application of machine learning methods in neuroimaging research has increased, especially with the aim to predict the onset of a full-blown psychotic disorder in individuals with at-risk mental states, or to predict poor outcome, independently from the conversion to psychosis. Effective prediction would allow the early identification of the specific subgroup of at-risk individuals that will benefit from preventive interventions[3-6].

Further important topics addressed in the book include the impact of antipsychotic medications on brain structure and function, links between genetic and neuroimaging research, as well as recent progress in the field of "imaging genetics".

All authors shared the view that the potential of neuroimaging research for translation into psychiatric clinical practice should now be tested. Further investigations with multicenter and multimodal imaging design, integrating clinical measures and imaging data, and applying new multivariate approaches, such as different combined machine learning algorithms, are needed to consolidate promising findings and finally add methods of precision psychiatry to current clinical practice.

All those who contributed to this book, including the authors of the present report, are grateful to the WPA for providing Section members with the opportunity to meet and exchange knowledge and experiences[7], and contribute to the progress of the many facets of psychiatry.

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Implementation of the Action Plan of the WPA Secretary for Publications

Following the principles of the WPA Action Plan 2017-2020[1,2] and the specific Action Plan of the WPA Secretary for Publications[3], progress has been made in the past few months around two main axes: a) the dissemination of evidence- and value-based knowledge and good practices in psychiatry and mental health, and b) the promotion of WPA publications.

Concerning the first axis, the implementation of the new WPA website[4] will allow us to provide an online open access to the books of the series *Anthologies in Psychiatry*, and particularly to those for which we have been requested to allow a reprint or a translation.

Various steps have been taken to refine the WPA policy concerning these publications. Additionally, the decision has been made to link up our website with journals of partner institutions and ask them for reciprocity.

Preliminary contacts have also been established to foster the online publication of commissioned manuals and textbooks on topics relevant to psychiatry and mental health. Colleagues interested in this project have been approached and are ready to accept the collaboration of WPA components to select topics and editors for future manuals and textbooks in already existing series.

Through our Secretary for Sections, preliminary contacts have also been taken with a well-established scientific journal (the *British Journal of Psychiatry*) to allow WPA to commission one or more annual reviews on current issues and new findings in psychiatry and mental health. WPA Sections will certainly be a major source for these reviews[5].

The WPA Secretary for Publications is actively looking for ways to increase the visibility of research from colleagues who, for personal or contextual reasons, cannot have access yet to the most prestigious journals but deserve to be supported. Specially targeted here are the young and promising investigators of less resourced research teams and those working in less favored scientific environments (e.g., in low- and middle-income countries).

To reach this objective, the idea has emerged to propose to selected regional psychiatric journals (e.g., one from each continent) to publish regularly (e.g., annually) a WPA appointed thematic supplement. This project is now entering its first phase. Contacts have been initiated with fully indexed regional journals produced in English which are likely to be interested to accept this project, feel ready to comply with its requirements and have a free online access. Jointly with these journals' editorial boards, we will then select the topics suitable for such thematic supplements, trying to favor those not already covered by WPA publications.

Editors will be appointed for each WPA issue. They will be asked to try to involve, as much as possible, young and talented regional researchers. Additionally, they will have to consider the possibility to include in their supplement a review of the research work implemented and published in the related region, including work not published in English. The objective is to give more visibility to research work that is rarely accessible to the English speaking psychiatric scientific community. Moreover, each WPA supplement will be disseminated worldwide using the WPA global network. This dissemination endeavour could include favoring translation, whenever possible, without extra cost for the WPA.

Concerning the promotion of WPA pub-

lications, we have drafted a set of rules on the conditions a publication has to meet to be granted the WPA logo. Considering the fact that the WPA may be engaged legally and scientifically by granting its logo, this draft proposes a set of requirements aimed at giving the WPA enough control on the book's editorial project and content. These conditions include a revision of the book project by the Executive Committee at a very early stage (topic, editors) and its involvement in the selection of the authors of the chapters.

In line with these requirements, we are considering several projects of books. Contrary to the widespread opinion that books are not of value anymore to disseminate scientific knowledge, we have received numerous proposals of books. These include the proposal of an international anthology of experiences of community-based services; a book on mental health and well-being; and a volume on the history of WPA, to be produced in an electronic version uploaded on the new WPA website.

Following the success of the session on new WPA-related books and other publications at the 17th World Congress of Psychiatry in Mexico City, a similar session has been scheduled at the World Congress of Psychiatry to be held in Lisbon in August 2019. More than 15 books have been already accepted for this special session, particularly through the WPA Scientific Sections, showing once more the persistent vitality of WPA-related publications. Notably, most of them are authoritative and comprehensive volumes bringing a state-of-the-art view on crucial topics within our discipline.

Michel Botbol
WPA Secretary for Scientific Publications

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Undergraduate psychiatric education: a snapshot of medical students across the world

The exposure to psychiatry during medical education can contribute to increase recruitment and retention in the specialty[1,2]. This is particularly important as psychiatry as a career choice seems to be on the decline worldwide[3]. Furthermore, while psychiatric education at the postgraduate level has been researched to some extent[4-6], very little is known about how this education is included in undergraduate curricula at the global level, and even less about how medical students actually receive it across the world.

To address this question, we asked medical students themselves to clarify the means they are taught psychiatry in their undergraduate courses, comparing differences across regions and countries. For this endeavor, the International Federation of Medical Students' Associations (IFMSA) and the WPA established a collaboration[7]. The IFMSA is the largest medical student organization worldwide, representing 1.3 million medical students from 125 countries.

An online survey was developed, which was circulated through the online platforms of the IFMSA to representatives of national member organizations. The questions in the survey explored whether psychiatry is included in the undergraduate curriculum, what is the duration of the practice and/or theory classes, and how the knowledge/competencies evaluation is made. The survey was conducted between March and May 2018.

Representatives from 83 countries responded (response rate: 66.4%). Psychiatry was reportedly included as a mandatory course in 81 out of 83 countries, and as an elective course in two countries (Ethiopia and Nigeria).

The reported duration of theory classes varied greatly: in 37 countries these lasted more than 30 days; in 29 countries 16 to 30 days; in 17 countries 1 to 15 days. The duration of practice classes was evenly distributed: 1 to 15 days in 29 countries, 16 to 30 days in 28 countries, and more than 30 days in 24 countries. Two countries (Nigeria and Burkina Faso) reported not having practice classes at all.

Comparing the results between world regions, countries from the Asian and Pacific region reported a shorter duration of education in psychiatry, while America seems to offer the longest exposure.

Moreover, different methods of evaluation of knowledge and competencies acquired seem to be used. Singular multiple-choice question-type (MCQ) testing was the most frequently reported method. In fact, it was a standalone evaluation method in 17 countries, and it was used amongst other methods in 57.

These findings show that worldwide countries do seem to recognize the importance of undergraduate psychiatric education, although clearly placing more emphasis on theoretical than on practical teaching. The same principle is applied in the evaluation process, as MCQ and summative assessment seem to be favored.

This worldwide survey targeting medical students is the largest ever conducted in terms of number of countries included, which is a major strength. Respondents were the representatives of national member organizations of the IFMSA, which have first-hand knowledge on whether and how psychiatric education is offered in their countries.

However, only 66.4% of national representatives responded, and it cannot be excluded that countries in which no undergraduate psychiatric education is provided could not be detected because their representatives did not participate in the survey. Furthermore, the respondents may not always have a full knowledge of their national situation, and there might be variations of psychiatric education across universities in the same country, which may have not been captured in the survey.

Still, this survey is an initial effort to

understand whether medical schools truly expose medical students to psychiatric education in the various countries of the world. It remains to be seen to which extent, if any, medical schools encourage students to opt for a career in psychiatry, especially considering the significant shortage of mental health workforce and its growing impact on global health[8].

We hope these findings may help to raise awareness of how psychiatric education is included in the curriculum of medical students across the world, from the perspective of those who receive it.

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