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EDITORIAL

Prospects and problems for a phenomenological approach to delusions

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In this issue of the journal, Sass and Byrom (1) outline some phenomenological accounts of delusion formation (highlighting experiences which, for simplicity, I will refer to as "altered reality experiences") and identify some points of contact with the relevant neuroscientific literature. As they freely admit, some of their ideas are speculative, but the general case that researchers should take the work of phenomenologists seriously is well made.

It is not difficult to perceive some common ground between the phenomenological approach and the cognitive-behavioural approach to delusions. For example, some of Conrad's case studies, as translated in an earlier paper by Bovet and Parnas (2) – e.g., case #3, in which a German soldier develops a paranoid illness after a series of failures and slights – are readily interpretable within a cognitive-behavioural framework, which emphasizes the importance of pre-existing cognitive biases and problems of self-esteem (3,4).

Freeman's model of paranoia, in particular, assigns a role to anomalous experiences in provoking the patient's search for meaning, and has been supported by studies showing associations between paranoia and sleep loss (5), cannabis use (6), hearing loss (7), and even a sudden reduction in height engineered in a virtual environment (8).

Hence, I think there is much to be gained from the cross-fertilization between different approaches to understanding delusions. Here I raise some questions about how this is to be achieved, echoing, to some extent, points previously made by others who have commented on the phenomenological approach to hallucinations (9).

Problems involved in reporting private experience have been long recognized in psychology and at one point led to a methodological version of behaviourism that ruled first-person reports of mental processes as illegitimate (10). Although few would take this extreme position today, the problem has not gone away. Seminal (11) and more recent studies (12) have amply demonstrated that people very often "tell more than they can know" about what is happening in their own minds.

Phenomenologists argue that their methodology is not compromised in this way because it differs in some important respects from introspection. Whereas the introspectionist attempts to obtain direct access to mechanisms, participants in phenomenological studies are instructed to report raw experiences, with all their assumptions and interpretations about those experiences "bracketed out" (13), conveying them to an interviewer whose relationship with the informant has been characterized as one of radical empathy (14).

Whether this distinction is always as clear as advertised is moot (phenomenological inquiries, it seems to me, often make inferences about mechanism). Even if it is, the phenomenological approach raises a more subtle difficulty that was discussed in the later philosophy of L. Wittgenstein (15) and clearly articulated by the radical behaviourist B.F. Skinner (16).

Contrary to some mischaracterizations of Skinner's position, he did not doubt that we can talk about private experiences, but was puzzled about how we are able to do so. Like Wittgenstein, he saw that language is the creation of a verbal community, and that learning how to describe, therefore, requires three elements: the individual, the stimulus to be described and (crucially) at least one other competent language user who also has access to that stimulus. Consider, for example, how we learn to identify simple physical objects such as furniture. If I call a chair a "table", I can be corrected if another member of the verbal community can see that I am looking at a chair. I can also be taught new verbal responses ("that is a chaise-longue"; or "a chaise-longue has the following features…"). These opportunities are denied in the case of experiences which only the speaker has access to, which is why so much of our language of experience is metaphorical – "a stabbing pain", "a heavy heart" (17). Even the word "depression" is a metaphor, stolen first by psychiatrists from cardiologists to signal the opposite of excitation before being passed onwards into everyday language (18).

Of course, phenomenologists are aware of the role of metaphor in experiential reports. Conrad's account of *trema* preceding the onset of delusions is explicitly metaphorical. Nonetheless, we are left with difficult questions about exactly what is happening when these reports are made. What kind of stimulus is being reported? And how are we to decide between different but apparently incompatible phenomenological claims such as those of, say, Conrad or Matussek? Without some kind of external criterion, these questions appear irresolvable.

A possible solution is to map phenomenological reports on to other kinds of data, for example, from neuroimaging studies, as suggested by Sass and Byrom and others before them (13). A minimum first step would be to address questions of reliability (the extent to which different interviewers elicit similar or different phenomenological reports). There has been some progress in this regard, for example, the

development of the Examination of Anomalous Self-Experience (19). Ultimately, this approach should lead to quantitative empirical investigations to determine in whom and in what circumstances altered reality experiences occur.

For some of the phenomenologists reviewed by Sass and Byrom, for example Jaspers, the answer to the "in whom?" question is "in people with schizophrenia". In principle, this claim could be analytical or synthetic. In the former case, what is being proposed is a narrow redefinition of schizophrenia which, I suspect, would be uncomfortable for many modern researchers. If the claim is synthetic, then empirical research is required to show that all (or at least only) schizophrenia patients (defined by some other criteria) suffer from these experiences.

A Danish study of 155 consecutive psychiatric referrals found that perplexity and abnormal self-experiences (similar to Conrad's *trema* concept) were reported by many but not all first episode schizophrenia patients (20). Another study (21) made the apparently spectacular discovery that 70% of non-psychotic patients with so called "basic symptoms" (mostly altered reality experiences) developed schizophrenia at long-term follow-up. However, this finding looks less spectacular when it is realized that two thirds were lost to follow-up. Assuming that these patients were most likely non-psychotic, the true conversion rate was probably about 25%. Further research along these lines would clearly be helpful.

However, an insurmountable difficulty is that schizophrenia is not a particularly coherent concept on *any* criteria that phenomenological data could be compared with. For example, family and molecular research shows a substantial shared genetic component with other diagnoses (22,23), clinical and neuroscientific data support a continuum with mood disorders rather than separate disease entities (24), and multivariate analyses of symptom data point to multiple, independent syndromes within the broad schizophrenia envelope (25,26). Hence, although Sass and Byrom express the hope that phenomenology might show "how syndromes (such as schizophrenia) can embody distinctive global modes of psychological life that may render symptoms (such as delusion) more heterogeneous than they otherwise appear" (1), it seems unlikely that phenomenological or, for that matter, any other kind of data could lead to a unified theory of schizophrenia. A much better approach would be to treat altered reality experiences as phenomena to be investigated in their own right.

The belief that altered reality experiences are indicative of schizophrenia has no doubt been fostered by the assumption that these experiences lie beyond the realm of normal mental life. However, we should be cautious in making this assumption, especially given recent evidence of continua linking psychosis to normal human experiences (27).

Altered reality experiences are typically elicited from patients during intensive questioning following a profound life crisis in which there is bound to be a search for meaning. This does not mean that they should be discounted, but it does mean that we should seek comparisons with the exceptional experiences of ordinary people, rather than with ordinary life. For example, we could compare the onset of psychosis with other sudden life changes such as religious conversion.

Indeed, religious conversion bares some similarity to delusion formation across a number of dimensions. For example, adolescence is a high-risk period for both (28). It has long been recognized that religious conversion, like the onset of delusions, often occurs against a background of personal crisis (29). Insecure attachment is a predisposing factor for both religious conversion (30) and paranoid delusions (31). There may be other similarities, for example, in terms of information processing and other kinds of psychological functioning. Some studies have reported difficulty in distinguishing between religious people and patients with delusions (32,33), although it is possible that the right questions were not asked.

If we should be wary of the assumption that delusions are different from other kinds of beliefs and attitudes, a corollary is that we should be mindful that much of ordinary mental life remains poorly examined. Hence, normal beliefs and attitudes may be much more complex than we usually suppose.

If phenomenological analysis is to shed light on abnormal mental states, perhaps it can begin by helping us to better understand the ordinary.

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EDITORIAL

Neural dynamics in mental disorders

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The search for the pathophysiological substrates of mental disorders remains an important challenge for psychiatric research. While major psychiatric conditions have a biological signature that can be identified with a range of neuroimaging approaches, biomarkers that allow reliable differentiation between different conditions as well as detection at early-illness stages have yielded only modest success. Given the importance of early intervention in a range of disorders as well as the move towards personalized medicine (1), understanding the underlying neurobiology is of crucial importance towards the development of more effective treatments and care.

While the difficulties in the field are also due to nosological overlap between different conditions and poor construct validity of major diagnoses, an impediment has also been the limited understanding and availability of measurement tools to gain insights into the complex neuronal dynamics in large-scale networks and their dysfunctions. In schizophrenia research, for example, the search for the underlying biological signatures of clinical symptoms and cognitive deficits had for a long time focused on the contribution of circumscribed brain regions, such as the prefrontal cortex. In contrast to this view, which was largely inspired by findings from clinical neuropsychology, current research suggests that anatomical alterations involve a large number of cortical and subcortical regions (2). On the basis of these observations and a large body of work highlighting a distributed neural and cognitive impairment, the hypothesis that I would like to advance is that schizophrenia and perhaps other mental disorders are likely to constitute systemic disturbances involving fundamentally a disruption in the dynamics of neural processes in large-scale networks (3).

This is supported by recent data which highlight that cognitive and executive processes during normal brain functioning essentially emerge from the coordinated activity of distributed neuronal populations that are dynamically configured on the backbone of fixed anatomical connections (4,5). The organization of anatomical connections and their contribution towards functional interactions is highlighted in the paper by Van Essen and Barch (6) in this issue of the journal, which summarizes recent advances in both structural and functional neuroimaging, in particular in mapping neural connections in terms of their structural and functional pathways, the so-called "connectome".

The brain's connectome has small-world properties (7), which implies that even neuronal groups distributed across distant cortical areas can communicate with one another either directly or via only a small number of intervening nodes. From this perspective, cognition, consciousness and their disturbances are not properties arising from isolated neuronal units but rather from the distributed and coordinated interplay of a large number of neuronal assemblies (5).

Evidence has accumulated that such neuronal coordination is achieved through modulating the synchrony of rhythmic activity at low and high frequencies. While neural oscillations have a long history in neuroscience, it was the discovery of Singer and colleagues that oscillations in the beta/gamma range (13-30/30-200 Hz) establish precise synchronization between distributed neural responses in the visual cortex (8), which led to the hypothesis that rhythmic activity at high frequencies constitutes a mechanism for establishing temporal windows for neuronal communication (9).

This perspective has contributed to the conceptualization of the brain as a self-organizing complex system in which numerous, densely interconnected but functionally specialized areas cooperate in ever-changing, context- and task-dependent constellations. Important and distinct variables of these dynamic processes are the power and frequency of oscillatory activity in local circuits and the long-range synchronization of these temporally structured activities across brain areas. Oscillatory processes, in particular at gamma-band frequencies, serve the generic cortical computations underlying local encoding of information, while long-range synchronization at low – theta (4-8 Hz), alpha (8-13 Hz) and beta (13-30 Hz) – frequencies serves the effective coupling between more remote brain regions (10).

Recent evidence has emerged that the pathophysiology of schizophrenia, but also of autism spectrum disorders and Alzheimer's disease, may fundamentally involve alterations in synchrony and amplitude of neuronal oscillations (neural synchrony) (11), highlighting that a disturbance in neuronal dynamics may lie at the core of these disorders. While it is currently unclear to what extent such impairments may be causal towards the pathogenesis of these syndromes, the hypothesis that changes in the precision and strength of neuronal oscillations are underlying the cognitive deficits and possibly certain clinical symptoms in several conditions is consistent with recent observations that schizophrenia and related disorders are characterized by alterations in the organization of the connectome (12), indicating that changes in the lay-out of cortico-cortical connections could impact on the establishment of large-scale functional interactions (see also 6 in this issue of the journal).

This perspective furthermore predicts that the mechanisms that are involved in assuring the generation of coordinated neuronal states are likely to be dysfunctional in mental disorders and thus could offer novel treatment targets and possibilities for early intervention. During normal brain functioning, networks of mutually interacting GABAergic interneurons are crucially involved as pacemakers in the generation of high-frequency oscillations in local circuits. In addition, AMPA- and NMDA-receptor mediated activation of GABAergic interneurons is essential for the generation of oscillatory activity and is involved in the long-range synchronization of spatially segregated cell groups (3).

Impaired high-frequency oscillations in schizophrenia but also in autism spectrum disorders are consistent with dysfunctions in GABAergic interneurons as a core impairment in these disorders (13). Moreover, animal models demonstrate that diverse genetic and environmental risk factors converge on specific defects in the development and function of interneurons (3), highlighting that such deficits constitute a critical pathway common to several syndromes which lead to impaired generation of rhythmic activity and cognitive deficits.

Data on GABAergic dysfunctions is accompanied by findings emphasizing the importance of aberrant glutamatergic neurotransmission in psychiatric conditions. In schizophrenia, hypofunctioning of the NMDA receptor is thought to be critically implicated in cognitive deficits as well as in psychotic symptoms, as blockade of that receptor can recreate many features of the disorder in human participants and animal models (14).

In order to further advance the role of aberrant neural dynamics in the explanation of major mental disorders and establish close links with underlying neurobiological parameters, a crucial prerequisite are non-invasive imaging tools that have sufficient temporal and spatial resolution. Until recently, studies investigating the spatial organization of large-scale cortical networks could only be conducted with functional magnetic resonance imaging (fMRI), because advanced source-analysis techniques for electrophysiological data which complement the excellent temporal resolution of electro/magnetoencephalography (EEG/MEG) were not available. However, recent studies which have mapped oscillatory cortical networks during cognitive and executive processes have demonstrated the feasibility of this approach, highlighting that modulations in the synchrony between brain regions are particularly crucial for cognitive processes (10).

While EEG/MEG approaches have the required temporal resolution to capture neuronal dynamics at realistic time scales, a distinct advantage of these approaches is also the fact that they are ideally suited for translational research. Neural oscillations and the molecular mechanisms and circuits that underlie them are highly conserved across a range of species (15), thus allowing hypotheses regarding the biological mechanisms that underlie impaired neural oscillations to be directly tested in animal models and *in vitro* preparations. This possibility may not be offered by other imaging techniques, such as fMRI, for which the biological mechanisms of signal generation are less clear and the direct translation of findings from data obtained with human experiments to animal models is more difficult.

Moreover, crucial insights into the pathophysiology of major mental disorders are also likely to require a focus on at-risk populations. Major psychiatric syndromes, such schizophrenia and Alzheimer's disease, involve an extended prodromal period prior to the full manifestation of clinical symptoms and diagnosis, during which cognitive impairments are already manifested. As the treatments available do not reverse circuits dysfunctions once clinical symptoms reach current diagnostic thresholds, development of biomarkers for targeted early intervention are crucial. EEG/MEG approaches may be ideally suited for this goal, as the wide range of oscillation frequencies provides a parameter space that can be used to delineate disorder-specific neuronal dynamics, which can then be used to identify the underlying pathophysiological mechanisms in pre-clinical research.

Moreover, such studies may also reveal insights into the neurobiology that may be closer to the essential core of mental disorders. For example, it is conceivable that certain clinical manifestations, such as the positive symptoms of schizophrenia, reflect the system's adaptive response towards a more fundamental disturbance in neuronal dynamics. From this perspective, genetic and environmental risk factors cause a primary disturbance that leads to a disruption of large-scale dynamics and cognitive dysfunctions. This view is consistent with previous formulations which have emphasized a differentiation between primary or basic symptoms and secondary or accessory phenomena in schizophrenia, the latter essentially representing compensatory and adaptive phenomena towards a fundamental disruption of neuronal processes.

While some of the issues raised in this paper reflect long-standing debates in both cognitive neuroscience and psychiatry with regard to the nature of brain functions and their disturbances, it is perhaps only now, with the increased knowledge and technology available to examine large-scale dynamics, that insights into the pathophysiology of mental disorders may be in reach. Such insights would not only be of tremendous value for scientific purposes, but also allow for more effective early intervention as well as for the development of rational treatments aimed at reducing the human and social costs associated with major mental disorders.

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Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder

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People with severe mental illness have a considerably shorter lifespan than the general population. This excess mortality is mainly due to physical illness. Next to mental illness-related factors, unhealthy lifestyle, and disparities in health care access and utilization, psychotropic medications can contribute to the risk of physical morbidity and mortality. We systematically reviewed the effects of antipsychotics, antidepressants and mood stabilizers on physical health outcomes in people with schizophrenia, depression and bipolar disorder. Updating and expanding our prior systematic review published in this journal, we searched MEDLINE (November 2009 - November 2014), combining the MeSH terms of major physical disease categories (and/or relevant diseases within these categories) with schizophrenia, major depressive disorder and bipolar disorder, and the three major psychotropic classes which received regulatory approval for these disorders, i.e., antipsychotics, antidepressants and mood stabilizers. We gave precedence to results from (systematic) reviews and meta-analyses wherever possible. Antipsychotics, and to a more restricted degree antidepressants and mood stabilizers, are associated with an increased risk for several physical diseases, including obesity, dyslipidemia, diabetes mellitus, thyroid disorders, hyponatremia; cardiovascular, respiratory tract, gastrointestinal, haematological, musculoskeletal and renal diseases, as well as movement and seizure disorders. Higher dosages, polypharmacy, and treatment of vulnerable (e.g., old or young) individuals are associated with greater absolute (elderly) and relative (youth) risk for most of these physical diseases. To what degree medication-specific and patient-specific risk factors interact, and how adverse outcomes can be minimized, allowing patients to derive maximum benefits from these medications, requires adequate clinical attention and further research.

Key words: Physical illness, cardiovascular, metabolic, endocrine, gastrointestinal, respiratory, schizophrenia, bipolar disorder, depression, antipsychotics, antidepressants, mood stabilizers

(World Psychiatry 2015;14:119–136)

People with severe mental illness (SMI), particularly schizophrenia, bipolar disorder and major depressive disorder, have an average mortality rate that is 2-3 times higher than the general population (1-3), corresponding to a 10-25 year shortened life expectancy (2-9). The most common causes of death in people with SMI are physical diseases (10).

Mental illness-related factors, unhealthy lifestyle choices, as well as disparities, not only in health care access and utilization, but also in health care provision, contribute to the poorer physical health outcomes in people with SMI (11). However, the use of psychotropic medications can further increase the risk of physical complications/disorders.

Thorough knowledge about the effects of frequently used psychotropic medications – antipsychotics, antidepressants and mood stabilizers – on physical health in people with SMI can inform better treatment choices and/or strategies.

Updating and expanding our prior review published in this journal (11), we systematically searched MEDLINE (November 2009 - November 2014) for epidemiological, morbidity and mortality data combining the MeSH terms of major physical disease categories and/or relevant diseases within these categories (Table 1) with schizophrenia, major depressive disorder and bipolar disorder, and the three major psychotropic classes which received regulatory approval for these psychiatric disorders, i.e., antipsychotics, antidepressants and mood stabilizers. While psychotropic medications can potentially increase the risk of many physical diseases, we focused on a selected number of diseases. We further restricted our search to pertinent English-language (systematic) reviews and meta-analyses, although for certain physical diseases relevant individual studies were selected.

The MEDLINE searches yielded 13,477 hits (Table 1). Below, we summarize the findings concerning the relationship of antipsychotics, antidepressants and mood stabilizers to each physical illness/domain.

NUTRITIONAL AND METABOLIC DISEASES

Obesity

People with SMI are, compared to the general population, at increased risk for being overweight and obese (12-15). The likelihood of being obese is increased 2.8-4.4 fold in patients with schizophrenia and 1.2-1.7 fold in those with major depression or bipolar disorder (16-22).

Weight gain – commonly assessed as body weight change, change in body mass index, or clinically relevant ($\geq$7%) weight change from baseline (23,24) – is a well-established side effect of antipsychotics during the acute and maintenance

Table 1 MEDLINE search results: disease category (+SMI, + psychotropic)

Nutritional and metabolic diseases: 1,958 hits (358 reviews)
Obesity: 1,550 hits (266 reviews)
Dyslipidemia: 408 hits (92 reviews)
Endocrine system diseases: 1,709 hits (324 reviews)
Diabetes mellitus/diabetic ketoacidosis: 1,305 hits (256 reviews)
Thyroid disorders/hyponatremia/SIADH: 404 hits (68 reviews)
Cardiovascular diseases: 1,394 hits (211 reviews)
Coronary heart disease/sudden cardiac death: 617 hits (85 reviews)
Cerebrovascular disease: 777 hits (126 reviews)
Hypertension/myocarditis: 965 hits (165 reviews)
Respiratory tract diseases
Pneumonia: 108 hits (11 reviews)
Gastrointestinal diseases
Liver diseases/constipation: 672 hits (150 reviews)
Neoplasms
Cancer: 2,387 hits (396 reviews)
Muscoloskeletal diseases
Osteoporosis: 163 hits (49 reviews)
Haematologic diseases: 364 hits (40 reviews)
Other diseases: 4,121 hits (890 reviews)

SMI – severe mental illness, SIADH – syndrome of inadequate antidiuretic hormone secretion

treatment of patients with schizophrenia, affecting 15 to 72% of these patients (11).

There is, however, a hierarchy for risk of weight gain among antipsychotics, that has been confirmed in different studies and meta-analyses (11,23-33). Weight gain is greatest with the second-generation antipsychotics (SGAs) clozapine and olanzapine, while quetiapine, risperidone, paliperidone and iloperidone have an intermediate risk. Aripiprazole, amisulpride, ziprasidone, asenapine and lurasidone have less or little effect on body weight (11) (Table 2), although observed effects depend on the degree of prior treatment exposure (30). In children and adolescents (<18 years old), roughly the same hierarchy for risk of weight gain with these agents has been identified (23,34-36), yet at a higher level, likely due to less prior antipsychotic exposure (30). Among the first-generation antipsychotics (FGAs), the so-called low-potency agents, such as chlorpromazine and thioridazine, have higher weight gain potential than the high-potency drugs, such as haloperidol (11,30).

No antipsychotic, however, should be considered truly weight neutral, as the proportion of individuals experiencing significant weight gain is greater with any SGA than with placebo (11,31). Antipsychotic-naïve or first-episode patients are more vulnerable to weight gain, as all antipsychotics have been found to cause significant weight gain in these patients (24). Moreover, antipsychotics have been found to produce more severe weight gain in these patients compared to those with chronic schizophrenia (37).

Generally, weight gain with antipsychotics is rapid during the first few weeks, slows gradually, and often reaches a plateau within one year (23). Results indicate that the first year of antipsychotic treatment is a critical period for weight gain and metabolic abnormalities (38), as initial rapid weight gain is a good indicator for long-term weight gain and obesity (23,39). According to a recent meta-analysis (24), almost all antipsychotics show a degree of weight gain after prolonged use, except for amisulpride, aripiprazole and ziprasidone. This meta-analysis also documented that switching subjects to metabolically more neutral compounds may not result in weight loss in all cases.

Antidepressants, such as amitriptyline and mirtazapine, and mood stabilizers, such as lithium and valproate, have also been associated with weight gain (23,40,41) (Table 2). However, weight gain is generally more modest or mild with antidepressants and mood stabilizers, and differences between antidepressants are modest (40).

Clinical and animal study data suggest that increasing appetite and food intake, as well as delayed satiety signaling, are key behavioral changes to antipsychotic-induced weight gain/obesity (24,39,42). Antagonism at 5-HT2C and H1 receptors seems involved in antipsychotic-induced weight gain. Among antipsychotics, clozapine and olanzapine, which have the highest weight gain/obesity risk, also have the highest affinities for 5-HT2C and H1 receptors (39).

There are marked individual variations in weight gain, irrespective of prescribed antipsychotic (39): some subjects lose weight, others maintain or gain weight with the same agent (24). Although (partial) non-adherence can be a confounder, this observation, together with the results from monozygotic twin and sibling studies, suggests that genetic factors play an important role in medication-induced weight gain (43-45), with estimates as high as 60-80% for antipsychotic-related weight gain (46).

Dyslipidemia

Antipsychotics have been associated with lipid abnormalities to relevant degrees (11,30) (Table 2). Adverse effects on triglycerides and cholesterol occur early and may even precede weight gain, pointing to weight-independent, molecular effects in addition to weight-related ones (30).

Compared to age- and sex-matched general population cohorts, metabolic syndrome criteria for elevated triglycerides (OR = 2.73, 95% CI: 1.95-3.83) and decreased high-density lipoprotein (HDL) cholesterol (OR = 2.35, 95% CI: 1.78-3.10) were more commonly met in patients with schizophrenia (17). Moreover, in chronic antipsychotic

Table 2 Adverse effects of antipsychotics, antidepressants and mood stabilizers on specific physical health outcomes

Physical disease/condition	Antipsychotics	Antidepressants	Mood stabilizers
Nutritional and metabolic diseases			
Obesity	0/+ (haloperidol, lurasidone, ziprasidone, aripiprazole) to +++ (clozapine, olanzapine, low potency FGAs)	− (bupropion) to + (mirtazapine, paroxetine, TCAs)	0 (lamotrigine) to ++ (valproate, lithium)
Dyslipidemia	+ to ++	0 to + (if weight gain)	− (valproate: cholesterol) to +
Endocrine system diseases			
Diabetes	0/+ (haloperidol, lurasidone, ziprasidone, aripiprazole) to +++ (clozapine and olanzapine > low and mid potency FGAs)	0 to +	0 to ++ (valproate)
Thyroid disorders	0	0	0 to ++ (lithium)
Hyponatremia/SIADH	+	+ to ++ (SSRIs)	0 to +
Cardiovascular diseases			
Hypertension	0 to ++	0 to + (venlafaxine)	0
Coronary heart disease and stroke	+ to ++	0 to +	0 to +
Myocarditis	0 to + (clozapine)	0	0
QTc prolongation/ sudden cardiac death	0 to + (thioridazine>sertindole > ziprasidone)	0 to + ?	0
Respiratory tract diseases			
Pneumonia	+ to ++ (clozapine)	0	− (lithium) to 0
Gastrointestinal diseases			
Constipation	0 to ++ (clozapine)	0 to + (TCAs)	0
Liver dysfunction	0 to ++ (often early and transient)	+	0 to ++ (valproate > carbamazepine)
Neoplasms			
Breast cancer	0 to + ?	0	0
Prolactinoma	0?	0	0
Musculoskeletal diseases			
Osteoporosis/fractures	0 to + (prolactin-raising antipsychotics)	+	− (lithium) to 0
Hematologic diseases			
Leucocytopenia/agranulocytosis	+ to +++ (clozapine)	0 to +	0 to ++ (carbamazepine)
Thrombocytopenia	0	0	0 to ++ (valproate)
Other physical diseases			
Kidney diseases	0	0	0 to ++ (lithium)
Movement disorders	+ to +++	0 to +	0 to +
Seizure disorders	+ to ++ (clozapine)	0 to + (TCAs > bupropion)	− to + (lithium toxicity)

− = reduction; 0 = likely/generally no effect; + = some effect; ++ = moderate effect; +++ = marked effect, ? = questionable

SIADH – syndrome of inadequate antidiuretic hormone secretion, FGAs – first-generation antipsychotics, SSRIs – selective serotonin reuptake inhibitors, TCAs – tricyclic antidepressants

treated patients, compared to first-episode or untreated patients with schizophrenia, metabolic syndrome criteria were more commonly met for elevated triglycerides (19.6% and 16.9% vs. 41.1%) and low HDL cholesterol (21.9% and 20.4% vs. 44.7%) (17). An elevated risk for meeting the triglyceride and HDL cholesterol criteria for metabolic

syndrome was also found in patients with depression (22) and bipolar disorder (47), with higher metabolic syndrome risk in populations receiving antipsychotics.

Although some antidepressants have been associated with weight gain (23,41), which is a risk factor for lipid abnormalities, data on adverse lipid effects of these medications remain scarce, and most antidepressants have not been associated with dyslipidemia (48) (Table 2).

Among mood stabilizers, lithium has not been associated with relevant lipid abnormalities (49), although lithium-induced hypothyroidism can lead to weight gain and changes in lipid profile (50). Valproate has been associated with reductions in total and low-density lipoprotein (LDL) cholesterol in patients with schizophrenia (51) and bipolar disorder (52), despite its association with weight gain, increased triglycerides and glucose, and insulin abnormalities (53) (Table 2).

ENDOCRINE SYSTEM DISEASES

Diabetes mellitus

Evidence suggests that the prevalence of type 2 diabetes mellitus (DM) in people with schizophrenia, bipolar disorder and schizoaffective disorder is 2-3 fold higher than in the general population (9,16,25,39,54,55). Two meta-analyses found overall prevalences of DM in people with multi-episode psychosis to be 9.5% (N = 116,751) (16) and 12.8% (N = 2,098) (56), respectively, nearly twice as high as in the general population (9). The risk of type 2 DM in people with (major) depression or depressive symptoms is 1.2-2.6 times higher than in those without depression (11,57). The age of onset of DM in individuals with a SMI seems to be about 10-20 years earlier than in the general population (58,59).

An association, albeit of uncertain magnitude, seems to exist between antipsychotics and DM, affecting about 12% of people receiving these medications (9). Recently, meta-analyses (16,56) showed that the prevalence of DM is not appreciably increased in drug-naïve patients during the first episode of psychosis once control groups are age-matched. The majority of studies suggest that metabolic abnormalities accumulate rapidly after the initiation of treatment (9,30).

Although a former meta-analysis showed that SGAs seem to have a stronger diabetogenic risk than FGAs, the risk being 1.3 fold higher in people with schizophrenia taking the former compared with those receiving the latter medications (60), a more recent meta-analysis indicated that, at the moment, evidence is still insufficient to draw firm conclusions about the relative risk of SGAs and FGAs (61). However, this uncertainty may well be due to the fact that neither of the two classes is homogeneous regarding cardiometabolic risk. Several studies suggest that the differing weight gain liability of SGAs contribute to the differing relative risks (RRs) of DM with these agents: specifically, olanzapine and clozapine, and to a lesser extent quetiapine and risperidone, were shown to be associated with an increased risk of glucose dysregulation or DM in people who have schizophrenia or bipolar disorder (28,62) (Table 2).

Nielsen et al (63) showed DM development in first-episode schizophrenia patients initially treated with olanzapine (hazard ratio, HR = 1.41) and mid-potency FGAs (HR = 1.60). During longer-term treatment and adjusting for follow-up duration, DM was associated with low-potency FGAs (OR = 1.45), olanzapine (OR = 1.57) and clozapine (OR = 2.31). Fleischhacker et al (64) found, in first-episode schizophrenia patients, newly diagnosed cases of DM with olanzapine and amisulpride during a 52-week treatment period.

Antipsychotics should be used with caution in children and youth (65). A recent study (66) found a 3-fold increased risk of DM in children and youth (the most frequently recorded psychiatric diagnoses were mood disorders, attention-deficit/hyperactivity disorder and conduct disorder) who had recently initiated antipsychotic treatment (HR = 3.03, 95% CI: 1.73-5.32), compared to those receiving other psychotropic medications. The risk was already increased within the first treatment year (HR = 2.49, 95% CI: 1.27-4.88), increased further with cumulative dose, and remained elevated one year after antipsychotic discontinuation (HR = 2.57; 95% CI: 1.34-4.91) (67).

Antipsychotics may induce DM independent of weight gain and adiposity (39,42). Thus, a model in which antipsychotic-induced DM is solely due to obesogenic effects is an oversimplification (42). These medications appear to contribute to DM both indirectly, by inducing weight gain, and directly, by promoting insulin resistance. M3 receptors play a crucial role in the regulation of insulin secretion through both peripheral and central cholinergic pathways (39). Therefore, DM induced by SGAs may be partly due to the blockade of central and peripheral M3 receptors. Olanzapine and clozapine, the SGAs with the highest risk to induce DM, also possess the highest M3 receptor-binding affinity (40). M3 blockade may lead to an initial disruption of insulin secretion and glucose homeostasis that can progressively lead to insulin resistance and DM during chronic treatment (67).

The literature is still inconclusive on a possible association between antidepressants and DM (23,68-71). Several reports (68,72-75) suggest that the (concurrent) use of (certain) antidepressants is associated with an increased risk of glucose dysregulation or DM; others do not (76,77) (Table 2).

A recent meta-analysis (78) found that antidepressants increased the likelihood of new-onset DM (OR = 1.50, 95% CI: 1.08-2.10; HR = 1.19, 95% CI: 1.08-1.32). However, because only observational studies were included in this analysis, a causal relationship could not be established (71,78). Long-term randomized controlled and prospective studies are needed to confirm a possible cause-effect relationship. Another problem is that (major) depression may

act as a confounding variable in the relationship between antidepressants and DM risk: antidepressants may have an impact on mental illness-related factors relevant to the risk for DM, such as physical activity and diet (71,79).

Nevertheless, there are indications that an increased risk of DM is associated with the concurrent use of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) (OR = 1.89) (80), the long-term use of either tricyclic antidepressants (incidence rate ratio, IRR = 1.77) or SSRIs (IRR = 2.06) in at least moderate daily doses (81), and the use of antidepressants in high-risk patients (82).

Some reports (57) also indicated that the use of mood stabilizers is associated with DM (OR = 1.64) in patients with major depression. Indeed, certain mood stabilizers, especially valproate, have been associated with an elevated risk for the development of insulin resistance (83) (Table 2).

Diabetic ketoacidosis

Although diabetic ketoacidosis (DKA), a potentially fatal condition (84), occurs most often in patients with type 1 DM (85), it may be the first obvious manifestation of type 2 DM. Physical symptoms include: increased thirst (polydipsia) and urination (polyuria), excessive appetite (polyphagia), nausea, abdominal pain and vomiting, dehydration, Kussmaul breathing, acetone ("fruity apple-like") breath, weakness or lethargy, confusion and alerted consciousness (85).

The incidence of DM presenting as DKA is, compared to the general population, nearly 10-fold higher in patients with schizophrenia (86). Cases of DKA in patients not previously known to be diabetic, including several fatalities, have been associated with SGA treatment initiation (54,86). While the underlying mechanisms are not well understood, antipsychotic-related DKA can occur soon after treatment onset and in the absence of weight gain (over one third of cases presented with either no weight gain or even weight loss) (85).

DKA can occur with almost all SGAs. However, at least half of the reports involve individuals on polypharmacy, complicating the risk attribution to a specific antipsychotic (85). The greatest number of DKA cases has been observed with clozapine and olanzapine. However, cases have also been reported with quetiapine, risperidone, and even with aripiprazole and ziprasidone (85,87), although order or channelling effects (i.e., shifting high-risk patients to lower risk agents) cannot be excluded.

Although DKA remains a rare adverse effect of SGAs, clinicians must remain vigilant, given its acute onset and potential lethality (85).

Hypothyroidism and hyperparathyroidism

Hypothyroidism is a common adverse effect of lithium, warranting continued monitoring (Table 2). A recent systematic review (40) concluded that, compared to placebo, lithium is associated with increased thyroid stimulating hormone (TSH) levels (+4.00 iU/mL, 95% CI: 3.9-4.1) and clinical hypothyroidism (OR = 5.78, 95% CI: 2.00-16.67).

In addition, lithium can produce adverse effects on the parathyroid gland. Compared with placebo, lithium was associated with increased parathyroid hormone (+7.32 pg/mL, 95% CI: 3.42-11.23) and blood calcium (+0·09 mmol/L, 95% CI: 0.02-0.17), but effects are generally mild (40).

Although quetiapine has been associated with mild T4 elevations, TSH levels were within normal limits and patients remained euthyroid (88).

Other antipsychotics, antidepressants, valproate and carbamazepine do not seem to affect thyroid or parathyroid functioning (Table 2).

Syndrome of inappropriate antidiuretic hormone secretion and hyponatremia

Antipsychotics appear to be associated with an increased prevalence of hyponatremia (89,90), which is often associated with polydipsia (Table 2).

Antidepressants, especially SSRIs, have been associated with the syndrome of inappropriate antidiuretic hormone secretion and with hyponatremia (91) (Table 2). In a recent systematic review (92), that was limited by variations in study designs, populations, and utilized thresholds, the incidence of hyponatremia diverged between 0.06% and 40% for SSRIs and between 0.08% and 70% for venlafaxine. Incidences for mirtazapine and tricyclic antidepressants were lower, and ORs for SSRIs (1.5-21.6) were consistently higher than for tricyclic antidepressants (1.1-4.9), but much less evidence was available for non-SSRI antidepressants. Identified patient risk factors included older age (OR = 6.3) and concomitant use of (thiazide) diuretics (OR = 11.2-13.5) (92). Carbamazepine and valproate have been associated with hyponatremia in case reports.

Based on the above, electrolytes should be checked in patients on antipsychotics, antidepressants and/or mood stabilizers with otherwise unexplained physical or mental state deterioration (Table 2).

CARDIOVASCULAR DISEASES

Hypertension

Although antipsychotics increase body weight and are associated with obesity, their effect on blood pressure is less pronounced than expected. This has likely to do with their alpha-1 blocking effects (93), which can lower blood pressure. Nevertheless, hypertension criteria for metabolic syndrome are more commonly met in patients with schizophrenia than in the general population (OR = 1.36, 95% CI: 1.21-1.53) (16), as well as in chronic patients with schizo-

phrenia receiving antipsychotics (39.7%) than in first-episode (30.4%) or untreated patients (24.3%) (56). Elevated risk for meeting the hypertension criterion for metabolic syndrome was also found in patients with depression (22) and bipolar disorder (47), with higher metabolic syndrome risk in populations receiving antipsychotics (Table 2).

Among antidepressants, venlafaxine is the one most frequently associated with increase in blood pressure (94), while mirtazapine has been found to be associated with hypertension less than tricyclic antidepressants (95) (Table 2). Generally, mood stabilizers do not affect blood pressure, unless chronic renal failure induced by lithium affects volume distribution (Table 2).

Coronary heart disease and stroke

The preponderance of evidence suggests that patients with schizophrenia, bipolar disorder and major depression are at significantly higher risk for cardiovascular morbidity and mortality than their counterparts in the general population (1,5,6,11,96-99). The risk is approximately 1.5 to 3-fold increased in patients with schizophrenia and bipolar disorder, and on average 1.5-fold increased in those with major depression. Moreover, cardiovascular diseases are the commonest cause of death in patients with SMI (100,101), with risks 10-fold higher than suicide (102). The literature on antipsychotic-related cardiovascular outcomes in patients with a SMI is sparse. Moreover, data are conflicting.

Although some studies (103,104) reported a higher risk of cerebrovascular diseases in patients using antipsychotics, others (105) did not (Table 2). In case-control studies with elderly patients, the probability of cerebrovascular accidents in antipsychotic users, compared with non-users, was approximately 1.3- to 2-fold greater (106). The risk of stroke is highest during the first weeks of treatment (104,106). A recent meta-analysis of 20 observational cohort studies found that older adults (≥65 years) using FGAs were not at a statistically significantly increased higher risk (RR = 1.4; 95% CI: 0.81-1.91) for stroke, as compared to SGA users (107).

Few studies have looked at the association between antipsychotics and myocardial infarction, which remains controversial because of heterogeneous clinical settings and methodological approaches (108,109). Some found an increased risk of myocardial infarction in older patients (≥66 years) with or without dementia (110,111) or patients with SMI (109,112) using antipsychotics compared to control subjects (RR = 1.15-6.2) (110,111). In the study by Lin et al (109), carried out in a large sample of patients with schizophrenia, mood disorders or dementia, the adjusted OR of acute myocardial infarction risk was 2.52 (95% CI: 2.37-2.68) for any antipsychotic, 2.32 (95% CI: 2.17-2.47) for FGAs, and 2.74 (95% CI: 2.49-3.02) for SGAs. A recent meta-analysis found that older adults (≥65 years) using FGAs were at higher risk for myocardial infarction (RR = 1.2; 95% CI: 1.16-1.23) compared to SGA users (107). However, several other studies (e.g., 112) found no significant association between the risk of myocardial infarction and antipsychotic exposure.

The risk for cardiovascular events varies with the individual SGAs. This risk seems to be lowest with aripiprazole and ziprasidone (113-115). Considering FGAs, a nationwide, register-based, five-year follow-up study of all patients presenting with first onset of schizophrenia found an increased likelihood for cardiovascular deaths among users of levomepromazine (OR = 2.68; 95% CI:1.37-5.25, p = 0.004) (116).

Data on the comparative acute cardiovascular safety of SGAs in younger adults are limited. In a recent large nationwide register-based cohort study (N = 48,625) (117), the risk of major cardiovascular events (cardiovascular mortality, acute coronary syndrome or ischemic stroke) in non-elderly (18-64 years) psychiatric outpatients was similar with risperidone, olanzapine and quetiapine within one year of treatment initiation. In another recent commercial U.S. claims database inception cohort study of 284,234 non-elderly adults aged 18-65 years (118), individuals within one year of exposure to SGAs showed a higher risk of essential hypertension (adjusted HR, AHR = 1.16, 95% CI: 1.12-1.21), DM (AHR = 1.43, CI: 1.33-1.53), hypertensive heart disease (AHR = 1.34, CI: 1.10-1.63), stroke (AHR = 1.46, CI: 1.22-1.75), coronary artery disease (AHR = 1.17, CI: 1.05-1.30), and hyperlipidemia (AHR = 1.12, CI: 1.07-1.17) than those exposed to antidepressants.

Compared to obese individuals without a SMI, obese patients with SMI have a significantly higher cardiovascular risk (119). This raises the possibility that, in addition to weight gain and obesity-related mechanisms, a direct effect of antipsychotics on cardiovascular risk may exist. For example, autonomic nervous system dysfunction triggered by schizophrenia may be exacerbated by antipsychotic treatment through blockade of peripheral dopamine receptors, increasing sympathetic activity (120). A direct effect of antipsychotics on insulin resistance, causing glucose intolerance, is another possible mechanism contributing to the increased risk of cardiovascular diseases (121).

The potential cardiovascular effects of tricyclic antidepressants are well known. They can cause orthostatic hypotension, slowed cardiac conduction, and increased heart rate, and are therefore best avoided in patients with pre-existing cardiovascular disease (122). SSRIs appear to have a better cardiovascular safety (123,124) (Table 2). Nevertheless, in patients with high risk factors, SSRIs (i.e., citalopram) (125,126) may be associated with (modest) QTc prolongation. Serotonin-norepinephrine reuptake inhibitors (SNRIs) are associated with a small, but increased incidence of cardiovascular adverse events (hypertension, tachycardia and orthostatic hypotension), while at therapeutic doses they do not seem to cause QTc prolongation (122). Although lithium can have some cardiac conduction effects, in general, it can be used safely in patients with cardiac disease (123) (Table 2).

Myocarditis

Myocarditis is a potential risk of clozapine treatment, occurring often early in treatment and in young male patients (127). Therefore, routine electrocardiographic monitoring for the first four weeks, and discontinuation of clozapine in the presence of myocarditis, may assist to prevent fatalities (128). However, case reports suggest that rechallenge with clozapine using slow titration may be successful in the majority of reported cases (129).

Sudden cardiac death

Patients with schizophrenia have been reported to be 2-4 times more likely to experience sudden cardiac death (SCD) than the general population (130,131). Although reasons for this increased risk remain unclear, individual susceptibility (e.g., underlying coronary artery disease (101) and higher prevalence of Brugada electrocardiographic abnormalities (131)) seems to be a relevant factor. Additional important risk factors include unhealthy lifestyle factors and psychotropic medications.

The association between SCD and specific psychotropic drugs has been explained by a lengthening of ventricular repolarization (QTc prolongation), predisposing the patient to life-threatening ventricular tachyarrhythmias (i.e., torsades de pointes, TdPs) (132). There is a consensus that QTc values $>$500 msec, or an absolute increase of $\geq$60 msec compared with drug-free baseline, puts patients at significant risk of TdPs and SCD (126,133). However, although a link exists between QTc and TdPs, this is neither linear, nor straightforward (126). Indeed, TdPs can occur at therapeutic doses of antipsychotics or antidepressants with a QTc interval $<$500 ms (134).

Patients using FGAs or SGAs have an increased risk of SCD compared to non-users with or without a psychiatric illness, with ratios ranging from 1.5 to 5.8, depending on the type of antipsychotic and restrictiveness of the SCD definition (11,131,135,136). The largest study to date (459,614 incident antipsychotic users) reported a SCD incidence of 3.4 per 1,000 person-years (137). Antipsychotics with a greater risk of QTc prolongation include thioridazine (greatest risk), pimozide, droperidol, mesoridazine, and i.v. haloperidol (total cumulative dose $>$ 2 mg) among FGAs (126,133), and sertindole, amisulpride and ziprasidone among SGAs (32,133). QTc prolongation with lurasidone and aripiprazole is judged to be clinically insignificant (32,133). QTc prolongation associated with asenapine and iloperidone is comparable to that associated with risperidone, olanzapine and quetiapine (32,133) (Table 2).

According to a recent meta-analysis, SSRIs are, compared to placebo, associated with a statistically significant (but clinically insignificant for most patients) dose-dependent increase in the QTc interval (+6.10 milliseconds; 95% CI: 3.47-8.73, $p<0.001$) (125). The highest effect seems to be associated with citalopram (138). Tricyclic antidepressants prolong the QTc interval to a greater extent than SSRIs by a factor of more than 2 (125).

Studies linking antipsychotics and antidepressants with an increased SCD risk suggest a dose-dependent relationship (135,139).

Cases of TdPs have been reported with antipsychotics, tricyclic antidepressants and SSRIs. Using the FDA Adverse Event Reporting System (FAERS) data, the Arrhythmogenic Potential of Drugs (ARITMO) project (140,141) classified, next to ziprasidone, five other SGAs (amisulpride, clozapine, olanzapine, quetiapine and risperidone) as having a very strong torsadogenic signal. However, these antipsychotics (with the exception of amisulpride and possibly quetiapine) have, in general, been associated with a QTc prolongation potential of questionable clinical concern (133). SSRI-associated TdP is a very rare event: only very few cases have been reported (142). However, adding SSRIs to SGAs may, although also very rarely, contribute to TdPs (143). There are no reported cases of lithium-induced TdPs (139).

Notably, coronary heart disease underlies the majority of SCD (144). A recent recommendation concludes that it is not mandatory to perform electrocardiogram monitoring as a prerequisite to initiating antipsychotic treatment in the absence of cardiac risk factors, unless the prescribed antipsychotic has been established to have an increased risk of TdP and SCD (133) (Table 2).

RESPIRATORY TRACT DISEASES

Pneumonia

One century ago, respiratory diseases, such as pneumonia and tuberculosis, accounted for the majority of deaths amongst people with SMI who lived in institutions (145). Today, they are still more prevalent in these individuals compared to the general population, and among the most common causes of death (146-149).

Not only having a SMI, but also the use of psychotropics is a risk factor for respiratory tract diseases. A dose-dependent increased risk for pneumonia is associated with current use of SGAs in patients with schizophrenia (adjusted RR, ARR = 1.69, 95% CI: 1.43-2.01 vs. non-users) (150,151) and bipolar disorder (ARR = 2.07, 95% CI: 1.58-2.71 vs. non-users) (152). Similarly, the current use of SGAs and FGAs in elderly patients without a SMI seems to be associated with a dose-dependent increase in the risk for pneumonia (153-157).

In patients with schizophrenia, particularly the current use of clozapine is associated with an elevated and dose-dependent risk of pneumonia (ARR = 3.18, 95% CI: 2.62-3.86, $p<0.001$), while this risk is moderate for olanzapine, quetiapine and risperidone (ARR between 1.32 and 1.83, $p<0.001$), compared to patients not currently using anti-

psychotics (150) (Table 2). In patients with bipolar disorder, the current use of clozapine (ARR = 2.59, $p<0.01$), as well as the current use of olanzapine and haloperidol, were associated with dose-dependent risk ratios for pneumonia greater than 2.50. Furthermore, pneumonia had a longer duration in these patients during the period of exposure to each of these drugs (151).

With antidepressants, no increased risk of pneumonia has been found in most studies (e.g., 158) (Table 2).

There seems to be no significant association between mood stabilizers and pneumonia, and lithium even has a dose-dependent protective effect (152) (Table 2). However, the combination of mood stabilizers and SGAs or FGAs was associated with an increased risk. Among drug combinations, olanzapine plus carbamazepine had the highest risk (ARR = 11.88, $p<0.01$), followed by clozapine plus valproic acid (RR = 4.80, $p<0.001$) (152).

Although the possible mechanisms of drug-induced pneumonia remain speculative (153), H1 antagonism by clozapine and olanzapine, inducing sedation, and M1 antagonism, inducing dryness of the mouth, esophageal dilatation and hypomotility, may be involved, as well as the additive sedating effect by carbamazepine or valproic acid (152).

GASTROINTESTINAL DISEASES

Liver diseases

Liver function test abnormalities in patients receiving antipsychotics are common, but often mild and transient. According to a systematic review (159), the median percentage of patients with any abnormal liver function test on any antipsychotic was 32% (range: 5-78%). However, the median percentage of patients with clinically significant elevations (i.e., > 3-fold above the upper limit of normal for alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase or > 2-fold the upper limit of normal for alkaline phosphatase) was 4% (range: 0-15%) (Table 2). Abnormalities were generally asymptomatic, arose within 6 weeks of starting an antipsychotic, and did not worsen or resolved with continued treatment. The most commonly abnormal liver function test involved transaminases, and there was no clear difference between FGAs and SGAs.

Rarely, antipsychotics have been associated with severe or fatal hepatic injury. The FGA chlorpromazine has been most widely implicated with severe cholestatic hepatic injury. There are three main mechanisms by which antipsychotics can be associated with liver injury: by impairing bile secretion, leading to cholestasis; by exerting a direct toxic effect on hepatocytes; and by affecting the liver indirectly via obesity leading to non-alcoholic fatty liver disease (159).

Between 0.5 and 3% of patients receiving antidepressants may develop asymptomatic mild elevation of serum aminotransferase levels. However, all antidepressants can induce hepatotoxicity, especially in elderly patients and those on polypharmacy (Table 2). The antidepressants with the highest risk of hepatotoxicity include iproniazid, nefazodone, phenelzine, venlafaxine, imipramine, amitriptyline, duloxetine, bupropion, trazodone, tianeptine and agomelatine (160-162). Those with the least potential include citalopram, escitalopram, paroxetine and fluvoxamine (162). Monitoring of liver function tests and immediate discontinuation upon emergence of abnormal laboratory findings or signs/symptoms of liver dysfunction are crucial, since most cases of hepatic damage are reversible when detected early (162).

Among mood stabilizers, carbamazepine and valproate have been associated with liver dysfunction and should be avoided in patients with pre-existing liver disease (163) (Table 2).

Constipation

Severe constipation leading to serious consequences and even death can occur with certain antipsychotics. The most reported complications are paralytic ileus, faecal impaction, bowel obstruction and intestine/bowel perforations (164).

Constipation has been most widely reported with clozapine (123,164), although it can be associated with other antipsychotics as well (165) (Table 2). The prevalence of constipation in randomized controlled trials is 39.6% with zotepine, 21.3% with clozapine, 14.6% with haloperidol and 12% with risperidone (166).

Constipation is a common side effect of tricyclic antidepressants, while it is not particularly associated with exposure to mood stabilizers (Table 2).

HAEMATOLOGIC DISEASES

Leucocytopenia and agranulocytosis

Antipsychotics (especially but not only clozapine), antidepressants (e.g., clomipramine and imipramine) and mood stabilizers (especially carbamazepine) have been associated with leucocytopenia and agranulocytosis (167-170) (Table 2).

Clozapine (particularly in the first three months of treatment) and phenothiazines are the most common causes of drug-related neutropenia/agranulocytosis (169). The risk for neutropenia and agranulocytosis with clozapine is approximately 3% and 1%, respectively, with older patients being at higher risk (167,168). Carbamazepine should not be used in combination with clozapine, due to its potentiation of neutropenia and agranulocytosis (169,170). Anti-infective agents, proton pump inhibitors and other gastrointestinal agents have also been associated with haematological adverse effects when co-prescribed with clozapine (171). Non-tricyclic antidepressants are rarely associated with agranulocytosis.

With appropriate management, the mortality from drug-induced agranulocytosis in Western countries is currently approximately 5% (decreasing from 10-16% over the past two decades) (167).

Thrombocytopenia

Among the reviewed psychotropic drug classes, only valproate has been associated with thrombocytopenia to a relevant degree (Table 2). The incidence may be around 5%, and more likely at valproate serum levels above 80 mcg/ml, especially in females and older people (172).

NEOPLASMS

Breast cancer

Generally, patients with SMI, especially schizophrenia, have lower cancer rates than the general population (173), despite unhealthy lifestyle and a higher likelihood of obesity. However, this comparison is complicated by the fact that most cancers accumulate with age and that people with SMI die on average 15-25 years earlier than the general population (11).

Breast cancer is one of the most commonly diagnosed cancers worldwide (one in eight women will be diagnosed with this cancer during their lifetime), is the leading cause of cancer death among females, and starts occurring in early adulthood (174-176). Given that women with schizophrenia have lower parity (177,178) and higher frequencies of other known breast cancer risk factors (obesity, DM, unhealthy lifestyle behaviors, including alcohol dependence and smoking), one would anticipate higher breast cancer rates in this population. However, data are conflicting. Although several studies have shown an increased breast cancer risk and mortality rate among women with schizophrenia (e.g., 173,179-182), other studies have found a decreased or a statistically non-significantly increased risk (e.g., 183,184) (Table 2). A recent meta-analysis of observational studies in people with central nervous system disorders found that patients with schizophrenia showed a higher co-occurrence of breast cancer (effect size = 1.25; 95% CI: 1.10-1.42) (185).

Increasing experimental and epidemiological data point to the influence of prolactin in mammary carcinogenesis (186), raising questions about the possible relationship between prolactin-raising antipsychotics and breast cancer risk. The current evidence base, however, is very limited. The majority of studies focused on patients treated with FGAs (186), not finding an increased breast cancer risk. An exception is the cohort study by Wang et al (187), in which 52,819 women on antipsychotic dopamine antagonists were compared with 55,289 women who were not on antipsychotics. The authors found that, compared with non-users, women who used antipsychotic dopamine antagonists had a 16% greater risk (AHR = 1.16, 95% CI: 1.07-1.26) of developing breast cancer, with a direct dose-response relationship. As stated by the authors, the magnitude of the observed risk, although statistically significant, was small in absolute terms (1,239 cases of breast cancer in the user group versus 1,228 cases in the non-user group). Furthermore, it was estimated that there is less than a 14% chance that a dopamine antagonist user who develops breast cancer does so on the basis of her antipsychotic use. The authors therefore concluded that their findings "do not warrant changes in patients' antipsychotic medication regimens" (187, p. 1153).

Among SGAs, there has been concern that risperidone, amisulpride and paliperidone, which have been associated with hyperprolactinemia (188), may increase the risk of breast cancer. However, so far, results indicate that these compounds do not seem to increase this risk (189).

A systematic review (190), including 93 studies (*in vitro*, animal and human studies) considering the effects of antipsychotics (FGAs + SGAs) on cancer development, found that these medications as a class cannot be considered as a risk factor for breast cancer in humans. Moreover, some reports describe mechanisms of cancer protection with antipsychotics (or antidepressants) (186,191,192). For example, it has been shown *in vitro* that (prolactin-elevating) phenothiazines may enhance the effect of tamoxifen, a first-line adjuvant treatment for breast cancer patients, in human breast cancer cells (193,194). Thus, to date, no robust evidence exists for an increased risk of breast cancer due to antipsychotic-induced hyperprolactinemia (186,195).

As evidence suggest that SSRIs can increase circulating prolactin above the accepted normal range (20 ng/ml in men and 25 ng/ml in women) (196-198) via prolactin releasing factors, such as vasoactive intestinal peptide and oxytocin (188), antidepressant-related breast cancer risk has been questioned. Overall, however, results do not support the serotonin-mediated pathway for the prolactin-breast cancer hypothesis, irrespective of the type of antidepressant (198-200) (Table 2).

Prolactinoma

Although a pharmacovigilance study raised concern about a possible association between prolactin-raising antipsychotics and prolactinomas (201), evidence for a causal relationship is missing (Table 2). Potential reasons for the observational association include a background rate of 5-10% of silent prolactinomas that are more likely detected when elevated prolactin levels prompt brain imaging studies, and the potential misclassification of pituitary hypertrophy related to prolactin elevation due to antipsychotics as prolactinoma (188). In patients with secreting prolactinomas and psychosis, the partial D2 agonist aripiprazole may be particularly useful (202).

MUSCULOSKELETAL DISEASES

Osteoporosis

Schizophrenia and bipolar disorder are associated with lower bone mineral density (BMD) and higher prevalence of osteoporosis compared to the general population (203-206). The etiology of BMD loss in these patients is complicated (204,207). Risk factors related to patients' lifestyle (e.g., smoking, reduced physical activity, alcohol abuse, vitamin D and calcium deficiency, polydipsia) (203), as well as use of antipsychotics (207,208), are likely to be involved. Several reviews and meta-analyses (209-213) have reported that (major) depression is also associated with low BMD and increased fracture risk.

Although raised prolactin levels induced by antipsychotics have been associated with an increased risk of osteoporosis (214) (Table 2), clinical data implicating antipsychotic-induced hyperprolactinemia as a possible major risk factor for bone loss remain limited and contradictory (203,204). One review (203) showed that 60% of the studies examining the relationship between antipsychotic-induced hyperprolactinemia and BMD loss found some effects of hyperprolactinemia. However, samples and effects were small, and only few studies were prospective. The increased risk for bone loss induced by hyperprolactinemia is believed to be mediated by hypogonadism (215), leading to abnormally low sex hormone levels, although some evidence suggests direct effects of prolactin on human osteoblasts (216).

Most studies and reviews (157,203,217-223) found significant increases in the risk of fractures (ORs between 1.2 and 2.6) associated with antipsychotics. Compared with SGAs, a higher fracture risk was found for FGAs in some studies (158,220,224), possibly due to extrapyramidal symptoms causing gait disturbances and impairing mobility and balance, which are risk factors for falls (and, thus, fractures) in older adults (107). However, other studies (105,219,225) found no differences between FGAs and SGAs. Moreover, it is also unclear whether individual SGAs differ in the risk of falls/fractures (105,218,226).

Longitudinal, cross-sectional and prospective cohort studies, as well as meta-analyses, suggest that antidepressants, particularly SSRIs, at therapeutic doses are associated with decreased BMD and increased fracture risk, especially in older adults (218,220-222,227-249) (Table 2). Reduced BMD has also been found in young adults and children prescribed SSRIs (250,251). For SSRIs and tricyclic antidepressants, a growing excess risk of fractures has been reported with increasing dose (227,233,235), although this effect does not appear to be homogeneous across the whole class of drugs (227). The increase in risk is highest during the early stages of treatment, with a dramatic increase after initiation, reaching a peak within one month for tricyclics and eight months for SSRIs (228), decreasing towards baseline following discontinuation (227,228).

The most recent meta-analysis (237), which pooled results from 13 qualifying cohort and case-control studies, found that SSRIs were associated with a significantly increased risk of fractures (RR = 1.72, 95% CI: 1.51-1.95, $p<0.001$). This increased risk was also observed in studies that adjusted for depression (RR = 1.74, 95% CI: 1.28-2.36, $p<0.001$) and for BMD (RR = 1.70, 95% CI: 1.28-2.25, $p<0.001$). Treatment with SSRIs seems also to be associated with an increased failure of bone implants, which suggests the need for careful surgical treatment planning in SSRI users (252). The effect of SSRIs on bone formation and resorption appears to be governed by the activation of a number of 5-HT receptors on osteoblasts and osteoclasts via endocrine, autocrine/paracrine and neuronal pathways (241,253,254).

Lithium is possibly associated with a reduced fracture risk (255,256) (Table 2). Long-term treatment with valproate combined with low-dose SGAs may adversely affect BMD in premenopausal women with bipolar disorder (257). Finally, concomitant use of an opioid with one or several antipsychotics may also increase fracture risk in elderly patients (258,259).

OTHER PHYSICAL DISEASES

Kidney diseases

Nephrotoxicity is a well-known side effect of lithium (260) (Table 2). Acute renal failure has been described in lithium intoxication (261), but the greatest concern is the possible progression to end-stage renal disease during long-term use (262).

However, conflicting evidence concerning lithium's effect on renal function exists. A systematic review (263), investigating the effects of lithium on renal function in older adults, and the largest and most recent meta-analysis to date (40), screening nearly 6,000 publications on various aspects of potential lithium toxicity in patients with depression or bipolar disorder, both concluded that there is little evidence for a clinically significant reduction in renal function in most patients, and that the risk of end-stage renal failure is low. These results are consistent with a former meta-analysis (264). Nevertheless, end-stage renal failure only starts appearing in some patients after continuous treatment for more than 15-20 years, whereas meta-analyses include numerous patients treated for shorter periods (265). Moreover, several studies (266,267) on prolonged lithium treatment have suggested that the risk of renal end-stage failure might not be that low.

According to the International Group for the Study of Lithium-Treated Patients, approximately 25% of patients on medium-term lithium therapy (<15 years), as well as most patients on long-term lithium treatment (>15 years), develop some form of chronic lithium nephropathy (268). However, this condition manifests primarily as impaired urinary concentration with or without polyuria, which generally has

little clinical relevance. In contrast, patients with severe polyuria are at increased risk for lithium intoxication due to fluctuations in sodium levels. Effects of lithium intoxication range from minor tubular changes to acute tubular necrosis, which generally is reversible upon removal of excess amounts of lithium. Recurrent lithium intoxication, however, is thought to promote progressive lithium nephropathy (269). Thus, regular lithium level monitoring may protect against acute and chronic renal failure, and should be mandatory in long-term lithium-treated patients (269).

Movement disorders

In susceptible patients, chronic treatment with antipsychotics can lead to movement disorders, including tardive dyskinesia, tardive dystonia and tardive akathisia (270) (Table 2). Although SGAs seem to have a 5- to 6-fold reduced risk for tardive dyskinesia compared to FGAs (271,272), the risk is not zero. Moreover, older people (273) and those with extrapyramidal symptoms or anticholinergic use (271) are at elevated risk for tardive dyskinesia.

Antidepressants, lithium and valproate are generally not associated with tardive dyskinesia (Table 2). Nevertheless, tremor and myoclonus, which can occur with lithium and valproate, respectively, can be mistaken for tardive dyskinesia. Moreover, movement disorders can also occur endogenously in patients with schizophrenia (274), and other medications, such as metoclopramide (275), also carry a risk for tardive dyskinesia.

Seizure disorders

All antipsychotics, especially clozapine, have the potential to reduce the seizure threshold (276,277). This effect is generally not clinically relevant, but is dose-dependent and rises sharply at clozapine doses of 500-600 mg/day, while relationships with clozapine blood levels are less clear (278). When seizures occur, this is not a reason to discontinue clozapine; rather, valproate should be added for seizure prophylaxis (adjusting the clozapine dose as needed) (127).

Antidepressants can also lower the seizure risk threshold (91,276), with intermediate epileptogenic potential for tricyclic antidepressants and lower epileptogenic potential for bupropion (277), which is still contraindicated in people with seizure disorders (Table 2). Being antiepileptic medications, valproate and carbamazepine reduce seizure risk, while lithium, which at lower doses may even be protective (279), can lead to seizures when reaching toxic levels.

CONCLUSIONS

Patients with SMI are at increased risk for physical diseases and related earlier mortality (11,280). Besides mental illness-related factors, disparities in health care access and utilization, and unhealthy lifestyle, psychotropic medications can contribute to the emergence or aggravation of physical diseases. This review summarized recent evidence for the effect of antipsychotics, antidepressants and mood stabilizers on physical health/illness in patients with schizophrenia, major depression and bipolar disorder.

In general, adverse effects on physical health are greatest with antipsychotics, followed by mood stabilizers, tricyclic antidepressants and newer antidepressants. However, effects vary greatly among individual agents, and interactions with underlying host factors are relevant. Higher dosages, polypharmacy, and the treatment of vulnerable (e.g., old or young) people seems to be associated with a greater effect on most physical diseases.

Although antipsychotics have the greatest potential to adversely affect physical health, it is important to note that several large, nationwide studies providing generalizable data have suggested that all-cause mortality is higher in patients with schizophrenia not receiving antipsychotics (4,281). Furthermore, clozapine (4), antidepressants (282), and lithium (283), as well as antiepileptics (284), are associated with reduced mortality from suicide. Thus, the potential risks of antipsychotics, antidepressants and mood stabilizers need to be weighed against the risk of the psychiatric disorders for which they are used and the lasting potential benefits that these medications can produce.

Nevertheless, greater attention to the possible impact of psychotropic medications on the physical health of people with SMI can aid clinicians in selecting appropriate treatments for individual patients whose medication-independent risk factors for specific disorders require special consideration. Moreover, knowledge about specific medication effects can help implementing appropriate monitoring and management strategies aimed at improving physical and well as mental health outcomes of these generally disadvantaged populations.

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The effectiveness of psychodynamic psychotherapies: an update

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This paper provides a comprehensive review of outcome studies and meta-analyses of effectiveness studies of psychodynamic therapy (PDT) for the major categories of mental disorders. Comparisons with inactive controls (waitlist, treatment as usual and placebo) generally but by no means invariably show PDT to be effective for depression, some anxiety disorders, eating disorders and somatic disorders. There is little evidence to support its implementation for post-traumatic stress disorder, obsessive-compulsive disorder, bulimia nervosa, cocaine dependence or psychosis. The strongest current evidence base supports relatively long-term psychodynamic treatment of some personality disorders, particularly borderline personality disorder. Comparisons with active treatments rarely identify PDT as superior to control interventions and studies are generally not appropriately designed to provide tests of statistical equivalence. Studies that demonstrate inferiority of PDT to alternatives exist, but are small in number and often questionable in design. Reviews of the field appear to be subject to allegiance effects. The present review recommends abandoning the inherently conservative strategy of comparing heterogeneous "families" of therapies for heterogeneous diagnostic groups. Instead, it advocates using the opportunities provided by bioscience and computational psychiatry to creatively explore and assess the value of protocol-directed combinations of specific treatment components to address the key problems of individual patients.

Key words: Psychodynamic psychotherapy, psychoanalysis, depression, anxiety disorders, eating disorders, somatic disorders, personality disorders

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Psychodynamic therapy (PDT) is on the retreat around the world in the face of critique of its scientific credibility. Empirically substantiated clinical judgement underpins professional accountability and transparency in health care and increasingly so in mental health (1). One would therefore expect empirically supported therapies to gradually replace treatment as usual in everyday clinical care (2-5). Many outside the cognitive-behavioural therapy (CBT) community have objected to this, raising concerns about the generalizability of findings from randomized controlled trials (RCTs) (6).

The issue of external validity of RCTs in the context of health care policy was recently exposed to philosophical scrutiny (7), leading to the suggestion that the key issue may not be the theory-driven question of whether an intervention works, but the implementation question "Will it work for us?". For example, multisystemic therapy for conduct disorder is supported by trials in the U.S. and Norway, but these results were not replicated in Sweden and Canada (8-19).

Along with other researchers, we have argued that, in order for a treatment to be considered as empirically supported, evidence beyond that provided by RCTs is required (20,21). However, this does not imply, as many have assumed, that RCTs can be replaced by methods that do not comply with Mill's "method of difference" maxim (stating that where you have one situation that leads to an effect, and another which does not, and the only difference is the presence of a single factor in the first situation, you can infer this factor as the cause of the effect) (22).

Some have argued that not only are RCTs for psychotherapy flawed because of issues of generalizability, but also that there are alternative ways of establishing psychotherapy as "evidence-based" (e.g., practice-based evidence) (23). However, it is misguided to deny that RCTs are key to establishing the validity of a therapeutic modality.

The history of medicine is littered with interventions that did remarkable duty as therapies and yet, when subjected to RCT methodology, were shown either to have no benefit over alternative treatments or even to prevent the patient from benefitting, in terms of effect size or speed, from a superior intervention. Perhaps the most dramatic example is the RCT that ended 100 years of radical mastectomies for breast carcinoma only 30 years ago. The study showed that half a million women who had been subjected to disabling, mutilating operations, performed with the best of intentions on the basis of a fallacious theory about how carcinoma spreads, could have had equally good outcomes with lumpectomies (24).

Empirical knowledge in psychological therapies is multifaceted and complex, and requires sophistication in the scrutiny of research data. While critical reviews that summarize or synthesize a body of research are not without value, they also have major limitations. They rely on the statistical significance of a study to determine an intervention's efficacy, yet statistical significance is primarily determined by sample size. Meta-analyses can pool multiple studies where each has low statistical power (a pervasive problem in psychotherapy research), but are potentially misleading when the RCTs being aggregated are not homogeneous in terms of the target population, the treatment method and the outcome measures. This is often the case for trials of PDT.

A recent meta-review of 61 meta-analyses covering 21 psychiatric disorders containing 852 trials and 137,126 participants yielded slightly larger effect sizes for psychotherapy

(0.58; 95% CI: 0.42 to 0.76) than pharmacotherapy (0.40; 95% CI: 0.28 to 0.52) studies (25), but the applicability of these figures is brought into question by the null results from head-to-head studies.

The limitations of meta-analyses have generated concern among a number of reviewers (26,27) that undue weight is given to heterogeneous small-scale studies, which are considered in preference to well-designed and well-conducted RCTs that converge in their results. While hard-pressed readers may understandably wish to take an intellectual short-cut to a pooled effect size rather than considering individual investigations, it is important to remember that meta-analyses lack individual patient data – they are based on response rates and mean values. This masks important heterogeneity that is often revealed by careful scrutiny of individual investigations.

This review has opted to prioritize individual studies. The key limitation of small studies is the so-called "file drawer" problem. Insufficient patients are sampled in small studies. As a consequence, relying on underpowered studies means that there is a risk that the likely effectiveness of a therapy is overstated simply because a study with the same sample size but chance negative findings is unlikely to have been published.

Further, it is important to recognize that the absence of a significant difference between two conditions in a study should not be considered evidence for equivalence. The latter requires a different statistical procedure and a larger sample size than the so-called "superiority trials" which most psychotherapy trials are (28). Lack of significant difference does not mean that two interventions are equally effective, but only that it is impossible to rule out their equivalence (29). A confident statement of superiority requires a trial with at least 50 individuals per arm for a medium effect size (30). Equivalence trials are expected to have sample sizes several times larger. Sadly, few of the trials which are reviewed here meet this elementary criterion.

Finally, how do we define psychodynamic psychotherapy? A recent meta-analysis likened the family of psychodynamic therapies to an actual, if somewhat dysfunctional, family whose many members hardly spoke to each other and sometimes even spoke different languages (31). This review uses a broad definition of psychodynamic treatment as a stance taken to human subjectivity that is inclusive and aimed at a comprehensive understanding of the interplay between aspects of the individual's relationship with his/her environment, whether external or internal (32). It refers to the extraordinary human potential for dynamic self-alteration and self-correction. This definition incorporates a developmental perspective, and assumes limitations on conscious influence, ubiquity of conflict, internal representation of relationships, mental defences, and that complex meanings can be attached to experience (32).

The boundaries of PDT have become blurred over recent decades by changes in both CBT approaches and psychodynamic theory and technique, leading to increasing convergence of both understanding and clinical methods, exemplified by the work of those around the boundaries of both domains (33-36). The common distinction between interpretive and supportive approaches (37) speaks to a clinical dichotomy that existed 30-40 years ago, but hardly applies today. Certain manualized treatments are labelled as psychodynamic (38,39), but a thorough content analysis of these remains to be done. The pragmatic approach adopted in this review has been to use self-declared allegiance as the guiding principle as to what constitutes PDT.

This review focuses on effectiveness and ignores questions of mechanism and treatment process. This was, again, a decision of expedience given the space limitations and the wish to provide a comprehensive survey. The literature search on which this contribution depends was based on the methodology evolved for two previous large-scale surveys (20,40) and involved a computer search of all major databases using 100 terms referring to different aspects of mental health problems and 11 terms describing psychotherapy (the search algorithm and full inclusion criteria are available on request). Studies were selected if they reported outcomes that were directly related to the disorder or to intermediate variables. The review is limited to experimental designs involving some degree of random assignment.

DEPRESSION

Short-term PDT

Several studies have compared PDT to waitlist (41,42), placebo (43-46) or usual care controls (47-50) in the short-term treatment of depression. The results are mixed, with some favouring PDT (41-43,47,49,51) while others report no superiority to controls (44-46,48,50).

A number of these studies are methodologically too weak to permit definitive conclusions, either due to small sample size (41-43,50) or because their implementation of PDT fails to meet criteria (52) for a *bona fide* treatment (44,48).

Among the good studies, results are still mixed. Some studies report medium effect sizes: −0.57 (95% CI: −0.99 to −0.14) (47) and −0.53 (95% CI: −0.92 to −0.13) (49). Perhaps the most rigorous study comparing supportive expressive therapy with placebo medication reported no superior effects at the end of treatment on either depression (45) or quality of life (46). However, a recent well-conducted study of women with depressive disorders and breast cancer found that significantly more of the PDT group achieved remission from depression than the usual care group (44% vs. 23%) (53). An RCT of a mixed anxiety and depression group also reported favourable post-treatment results for PDT on clinician and self-report measures (54).

An intriguing meta-analysis of studies carried out in China lists six controlled trials that reported substantial treatment success from psychodynamic psychotherapy as an adjunct to medication and conventional nursing in the treatment of depression in patients with Parkinson's disease (55).

Since in clinical practice psychological therapies for depression are mostly offered in combination with medication, the potential value added by brief dynamic therapy is a key question for practitioners. A well-constructed, appropriately powered RCT found combined treatment to be more acceptable (reducing refusal and premature termination of medication) and associated with higher recovery rates (41% vs. 59%) (56). These findings were confirmed for self-reported depression and quality of life outcomes, but not for clinician-rated outcomes (57). A further smaller study comparing clomipramine with or without PDT reported reduced depression, lower hospitalization rates, better work adjustment and better global functioning in the combined treatment group (58). A combined analysis of three RCTs (56,59,60), in which data were pooled to enable contrasts between pharmacotherapy alone and combination treatment, yielded better observer-rated and self-reported outcomes in terms of remission and response rates at treatment termination for combination treatments (61).

There may be moderators of the superior effect of combination treatments. So far, unreplicated findings suggest that PDT may be particularly indicated if depression is accompanied by personality disorder (62,63) or childhood trauma (64), and findings are restricted to long-term follow-ups (42,65,66). Dose-effect relations associated with the length of therapy (8 vs. 16 sessions) have not been found for combination treatments (59).

When pharmacotherapy is contrasted head-to-head with PDT, studies fail to identify differential effects (45,46,67,68). Adding pharmacotherapy to PDT brings equivocal benefit (60), an important observation in the light of consistent findings of patient preference for PDT (69). A meta-analysis comparing psychotherapies to treatment with selective serotonin reuptake inhibitors demonstrated that the former were comparable to medication and that PDT was as efficacious as other therapies. However, psychotherapies that were not *bona fide* (i.e., those delivered by professionals without substantial training in psychotherapy) had significantly worse outcomes (70).

Several high-quality trials reported comparisons between CBT and PDT. A well-powered equivalence trial (N=341) reported no observer-rated, patient-rated or therapist-rated differences at treatment termination or follow-up, although overall the remission rate was low at 22.7% (71-73). Another trial found PDT, but not counselling or CBT, to be superior to a control in reducing the rate of postnatal depression at termination (49), although the treatments were equivalent at short-term and long-term follow-up. By contrast, an RCT of 291 inpatients reported that CBT was equally effective in those selected for CBT or PDT, while PDT benefitted only those who were specifically selected for that treatment (74). Consequently, CBT was superior for the randomly rather than systematically assigned group of patients (75).

Earlier studies tended to show negligible differences between PDT and CBT, but the trials were too small and reporting too limited to permit reliable inferences about equivalence or even superiority (76-82). If CBT is superior to PDT, it is so only in very brief (8-session) implementations (77). PDT and solution-focused therapy appear comparable in effectiveness (83).

A recently advanced innovative approach used the Internet to deliver PDT based on a self-help manual in a programme lasting 10 weeks. Compared to a structured support condition, recovery rates of 35% vs. 9% were reported, which were maintained at 10-month follow-up (84). A second trial based on a different model also yielded good outcomes compared to online therapist support without treatment modules in a mixed mood and anxiety disorder population (85).

Long-term PDT

In normal practice, PDT is often offered as a long-term (50 sessions or more) treatment. However, only a handful of studies have explored the effectiveness of long-term PDT.

The Helsinki study showed long-term PDT to be inferior to short-term PDT initially, but superior after 3-year follow-up (86-88). In an intriguing comparison between intensive long-term PDT (psychoanalysis), long-term PDT and short-term PDT, psychoanalysis was initially inferior to both other therapies, but was more effective at 5-year follow-up (89).

A large-scale naturalistic study randomized 272 depressed patients to unmanualized long-term PDT, fluoxetine or their combination for 24 months (51). Long-term PDT on its own or in combination was more effective in reducing depression scores than fluoxetine alone, with a medium effect size.

A study in which participants with major depressive disorder were randomized to psychoanalysis or long-term PDT found significant superiority of psychoanalysis on self-rated measures of depression at 3-year follow-up, but no differences at 1 and 2 years (90). A quasi-experimental comparison found psychoanalysis but not long-term PDT to be superior to CBT on measures of depression at 3 year follow-up (91).

A recently completed study of 18 months of once-weekly psychoanalytic psychotherapy for patients with two previous documented treatment failures reported the psychotherapy to be superior to U.K. practice guidelines-based treatment, but superiority was not apparent until 2 years after the end of treatment (92).

Meta-analyses

Meta-analytic findings on the whole reveal large pre-post treatment effects (93,94) for PDT maintained at 1-year follow-up, with medium effect sizes indicating superiority to inactive controls (31,95) but either no difference (31) or slight inferiority (94) in relation to alternative interventions post-treatment. Checking for publication bias revealed the existence of "file drawer" studies favouring PDT, which abolished the inferiority.

Effect sizes at follow-up relative to other treatments are insignificant overall (31,94,96), but PDT performed significantly worse against CBT (31) and in geriatric studies (31). PDT is comparable to alternative treatments at long-term follow-up. It also increases the effect of antidepressant medication (31,96).

Comment

On the whole, evidence supports the use of PDT in the treatment of depression, although its effects compared to placebo and other inactive control treatments are moderate rather than large. There is evidence that the effects are maintained in both the short and long term. PDT may be a preferred alternative to pharmacotherapy and certainly adds to the effectiveness of medication. If CBT is more effective than PDT, this difference is neither large nor reliable. However, there are too few large-scale trials to fully establish equivalence.

The dynamic therapies considered under the heading "PDT" are probably quite similar in practice, but vary in theoretical orientation, content focus, and style of delivery (supportive vs. confrontational), and no single type of PDT emerges as particularly efficacious. The literature on long-term PDT, which is still in its infancy, suggests that this approach may have value, perhaps particularly with more complex and chronic cases of depression. There is a question over the issue of cost-effectiveness of these therapies. Both established and currently emerging Internet applications of PDT are of particular interest, because of their potential for efficient dissemination.

ANXIETY

Short-term PDT

Notwithstanding the high lifetime prevalence of anxiety disorders (97), few studies have examined the effectiveness of PDT for these conditions.

PDT has been shown to be superior to enhanced waitlist for social anxiety and social phobia (98-102). The most recent study, with 207 PDT and 79 waitlist patients, yielded large differences in remission rates (26% vs. 9%) (100). A smaller study showed that adding group PDT to medication (clonazepam) reduced social anxiety (103) and immature defence styles (104).

Whilst short-term PDT outperformed applied relaxation, it was equivalent or inferior to prolonged exposure in two small, early studies (98,99). More recent trials contrasting PDT with CBT found small between-group differences in remission (100,102). Continuous measures of phobia favoured CBT at termination. Between 6-month and 2-year follow-up, the differences between the two treatments disappeared (105).

A health economics study reported that the end of treatment cost-effectiveness of CBT and PDT compared to waitlist was uncertain and depended on societal willingness to pay (WTP): CBT proved cost-effective at WTP $\geq$ €16,100 per responder and PDT at WTP $\geq$ €27,290 (106).

There are no studies of PDT against inactive controls in generalized anxiety disorder, except a study of Internet-based PDT, which yielded no evidence of superiority to waitlist control on anxiety ratings (107). An early study of a poorly specified PDT showed it to be inferior to both anxiety management training and cognitive therapy at termination and short-term follow-up (108). A small study comparing PDT to supportive therapy failed to find superiority of PDT for interpersonal problems (109). An RCT contrasting CBT with PDT found the former to be superior on self-reported measures of anxiety, but this was not confirmed by independent observer ratings (110). At 12-month follow-up, significant differences favouring CBT remained on two of the measures (110).

Two small studies of panic disorder have been reported. In one study, panic-focused PDT was clearly superior to applied relaxation (73% vs. 39% response) (111), specifically for those with comorbid personality disorders (112). A similar study contrasted this treatment with CBT and found no significant differences, although a larger sample with the same response ratios (47% PDT vs. 72% CBT) would lead to statistical significance (H=0.52) (113).

There is no evidence that PDT is helpful for obsessive-compulsive disorder (114). The single study adding PDT to pharmacotherapy reported no significant clinical effect from this supplemental treatment (115).

There is only one study of PDT as an approach to post-traumatic stress disorder (PTSD) (116), which shows a significant reduction of intrusion and avoidance compared to waitlist, to about the same extent as hypnotherapy and trauma desensitization. Systematic reviews found insufficient evidence in relation to PTSD to warrant comment (117-119), although strong theoretical and clinical arguments have been advanced for incorporating a psychodynamic approach into PTSD treatment programmes (120).

Meta-analyses

Meta-analyses have tended to combine different anxiety disorders when providing effect sizes (31,121). PDT is reported to be significantly more effective than inactive control conditions with a medium effect size, and to be overall insignificantly different when compared with alternative treatments. However, substantial heterogeneity is reported in both primary and secondary outcomes. These conclusions differ from those of other reviewers (122,123) who compared PDT only with CBT and claimed definite superiority for the latter. This claim, however, has been questioned (121) and significant errors may indeed have crept into one of the above meta-analyses (122).

Comment

The effectiveness of PDT for anxiety is crucial in the debate between those who argue for specific treatment approaches, as in CBT, versus those who support a generic approach seeking to identify similar unconscious content across diagnostic groups.

In relation to social anxiety and perhaps generalized anxiety disorder and panic disorder, promising emerging evidence supports the argument for a generic approach. The case is weakened, however, by the absence of evidence for PTSD and the evidence of absence of effect for obsessive-compulsive disorder. In general, the methodological weaknesses of earlier studies call meta-analytic findings into question.

Overall, there is considerable potential for further sound research aiming to identify the anxiety conditions for which PDT may be particularly helpful.

EATING DISORDERS

A small study showed self-psychology oriented PDT to be superior to nutritional counselling in treating a combination of anorexia and bulimia nervosa. The comparison with an active treatment in the same study (cognitive orientation therapy) favoured PDT, particularly for bulimia nervosa (124). By contrast, two studies focusing on bulimia nervosa found both PDT and CBT to be effective in reducing eating disorder symptoms, but CBT was slightly superior on global measures of clinical outcome, self-rated psychopathology and some indicators of social adjustment (125,126).

A 16-week course of group psychodynamic psychotherapy for binge eating disorder was superior to treatment as usual on all measures, and mostly equivalent to group CBT in reducing binge eating and overall improvement (79% PDT vs. 73% CBT) (127). PDT resulted in lower depression and more improvement in self-esteem, but greater susceptibility to hunger. There was some indication that patients with higher attachment anxiety benefitted more from PDT.

A recent report of an RCT of 70 patients with bulimia nervosa, contrasting 2 years of once-weekly PDT with 20 sessions of CBT over 5 months, found CBT to be more effective in both the short (5 months) and long (2 years) term (128). Both treatments were effective in reducing eating disorder symptoms and general psychopathology. On the face of it, this finding might be considered to have appropriately challenged the value of PDT, except that, strangely, this manualization of PDT precluded addressing bingeing and purging *unless the topic was volunteered by the patient* (129). The findings drew attention to the importance of adapting PDT to the patient's presenting problems (130).

An RCT comparing focal PDT with family therapy, cognitive analytic therapy and routine treatment of anorexia nervosa found that PDT achieved more improvement (52%) than routine treatment (21%) and achieved outcomes comparable to family therapy (41%) and cognitive analytic therapy (32%) (131).

In a recent, exceptionally high-quality study (Anorexia Nervosa Treatment of OutPatients, ANTOP) (132,133), focal dynamic psychotherapy was contrasted with enhanced CBT and treatment as usual, which incorporated the same intensity of psychotherapy, offered by community experts. Weight gains were comparable across the three groups over 12 months. With respect to global outcome measures, patients allocated to PDT had higher recovery rates than the control group; this was the first study to show superiority to CBT. Patients in the control group more frequently required inpatient treatment (41%) than those receiving PDT (23%) or CBT (35%). Although full syndrome anorexia nervosa persisted in 21% of PDT patients (versus 28% of controls), the findings, in association with other studies (134), suggest that a focus on intra- and interpersonal factors is beneficial for individuals with this disorder (135).

PDT in the treatment of anorexia nervosa in 12-19-year olds was found to be comparable to family-based treatment after 12-18 months of implementation in terms of achieving a target weight, but slightly inferior in terms of change in body mass index and more frequent hospitalization (136,137). In an independent study of PDT versus family-based therapy, age appeared to be a significant moderator, with older patients benefitting more from individual therapy and younger patients from family-based approaches in both short-term (138) and long-term follow-up (139). A definitive study with larger samples found that, even for older adolescents, family-based treatment achieved higher rates of remission and larger treatment effects than individual treatment (140).

Comment

There is strong evidence (two independent RCTs, one of which is large) that PDT can contribute to recovery from anorexia nervosa. This is underscored by the fact that treatment as usual in the ANTOP trial included psychotherapy, which, given the location of the study (Germany), was most likely to have been non-manualized PDT.

While available studies are small and conflicting, there is sufficient uncertainty about the relevance of PDT for bulimia nervosa to warrant further research in which the implementation of the therapy is more appropriately symptom-focused.

SOMATIC PROBLEMS

A number of studies have examined the usefulness of interpersonally oriented PDT for individuals presenting with a range of pain symptoms.

A relatively large study of irritable bowel syndrome patients, randomized to usual (medical) care or PDT (plus usual care), reported substantial changes in somatic symptoms, abdominal pain and bowel dysfunction at 3 and 15 months in the PDT group (141). A 12-week trial found that women presenting with irritable bowel syndrome benefitted more from PDT than from active listening in terms of self- and doctor-rated symptoms (142). Those in the control group who accepted psychotherapy after the end of treatment improved, and those who declined relapsed.

A further study with people with the same clinical problems contrasted eight sessions of PDT with pharmacological treatment (paroxetine) and treatment as usual (143). Both active treatments reduced physical distress but neither improved pain ratings. Psychotherapy reduced health care costs during the follow-up year. Patients with a history of sexual abuse particularly benefitted from PDT, but those with depression did better with paroxetine treatment.

A comparison of PDT with supportive psychotherapy in patients with dyspepsia reported that at 1 year 54% felt physically much better with the former treatment, compared to 28% of those receiving the latter (144). The physical improvements were in line with improvements in psychological symptoms in the PDT group. These findings were replicated in a small Iranian RCT, indicating cultural generalizability (145).

A well-powered trial in patients with chronic pain symptoms, randomized to PDT or enhanced medical care, yielded medium between-group effects (d=0.42) for physical quality of life at 9-month follow-up (146). An earlier study with a smaller sample of patients with somatoform pain disorder and a much longer (33 sessions) treatment also yielded significant pain reductions, in addition to improvements in somatization, mood and social adjustment (147).

An evaluation of 25 sessions of PDT compared to four consultations over 6 months for patients with fibromyalgia found no evidence of superiority of PDT for symptoms specific to this disorder or general psychiatric problems (148). However, the training offered to the therapists was brief (4 hours) and focused on insight rather than interpersonal emotional awareness, which has been found to be more relevant (149).

An imaginative study randomized general practitioners to be trained to work jointly with psychodynamic psychotherapists to deliver 10 weekly group therapy sessions in addition to the diagnosis and psychological management of medically unexplained symptoms (150). This large trial found significant small to medium health benefits over enhanced medical care from this psychodynamic group intervention.

A large quasi-experimental study compared pre- and post-treatment health care costs for 890 patients treated with brief PDT for a broad range of somatic and psychiatric disorders with those of a control group (N=192) who were referred but never treated, and found an average cost reduction per treated case of $12,628 over 3 follow-up years, with significant differences between groups for follow-up hospital costs (151).

Meta-analyses

No meta-analyses have been reported recently. A limited review identified only 13 RCTs and a moderate effect size for somatic symptoms (d=−0.59; 95% CI: −0.78 to −0.40), but the random effects model failed to reach significance (152). The effects are clearer for psychiatric symptoms and social adjustment than somatic symptoms.

Comment

The evidence base for PDT in somatoform disorders compared to control treatments is quite robust. Although there are no adequate meta-analytic summaries, this narrative review clearly reveals that an interpersonal form of dynamic therapy has substantial and relatively long-term effects, with medium effect sizes compared to enhanced treatment as usual, and that PDT may be able to reduce long-term health care costs for somatic disorders.

Interestingly, there appear to have been no comparisons with active symptom-focused psychosocial treatments such as CBT. Yet, a comparison may be relatively easy, since in this context PDT is mostly offered as a particularly brief intervention (8-10 sessions).

The overall impression is that PDT may be more effective when somatoform disorders are associated with adverse social histories rather than manifest psychiatric problems.

DRUG DEPENDENCE

RCTs suggest that the value of PDT in the treatment of drug dependence is moderated by the substance involved. An early study of methadone-maintained opiate dependence found drug counselling plus either supportive-expressive PDT or CBT to be beneficial relative to drug counselling alone, but there were no differences between the two psychotherapies (153-155). Patients with psychiatric morbidity benefitted most from the psychotherapies (156). A replication study of methadone users with psychiatric morbidity contrasted only PDT with counselling and observed a reduction of cocaine-positive but not opiate-positive urine samples during the treatment period (157). Importantly, this study demonstrated better maintenance of abstinence at 6 months, lower-dose methadone use and a significant reduction in psychiatric morbidity.

A study of cocaine dependence, contrasting CBT, PDT and individual drug counselling based on the 12-step philosophy (all incorporating group drug counselling) with group drug counselling alone, found individual drug counselling to be most efficacious (158). Neither CBT nor PDT added

benefit to group drug counselling, and they did not differ from each other in terms of effectiveness. Thirty-eight percent of individual drug counselling patients compared to 18% of PDT patients maintained 3 months of consecutive abstinence. However, individual drug counselling did not reduce psychiatric symptoms, unemployment, or medico-legal, social, alcohol or interpersonal problems to a greater extent than the other treatments (159).

Comment

It is unclear whether PDT should be recommended to supplement the treatment of opiate-dependent individuals. Individual drug counselling clearly has benefit and, since contingency management has become a preferred treatment for dependency problems (20,40), the role of PDT in the treatment of drug dependence is currently doubtful.

PSYCHOSIS

A Cochrane review of individual PDT for schizophrenia and severe mental illness, including four randomized trials with 528 participants, found that patients who had received PDT used less medication, were no more or less likely to be rehospitalized, but were less likely to be discharged (160). There was no clear evidence of any positive effect of PDT and adverse effects were not considered. Another meta-analytic review (161), which identified 37 studies with 2,642 patients, incorporated many studies from the 1950s to the 1970s, when treatment pathways and practices were quite different, which makes the pooled estimates impossible to interpret.

In a partial RCT, the Danish National Schizophrenia Project (162), patients with first episode psychosis received one of three treatment packages: one including PDT, the second multi-family treatment, and the third treatment as usual. Only a small subgroup of patients was randomized. When controlled for drug and alcohol use, the 1-year comparison revealed benefit from PDT (162). A further analysis after 2 years contrasted treatment as usual (N=150) with PDT (N=119) (only 72 patients had been randomly allocated). Patients receiving PDT had higher Global Assessment of Functioning scores (medium effect size) (163). Benefits were no longer evident at 5-year follow-up (164).

A pilot study of psychodynamic art therapy vs. treatment as usual with a small sample found a post-treatment reduction in positive psychotic symptoms, which dissipated 6 weeks later (165).

Comment

There is increasing optimism about the value of psychological therapy for psychosis, although the supporting evidence is limited even for CBT. The available evidence for PDT suggests some possible immediate benefit from dynamic approaches, but benefits are not sustained in the longer term.

PERSONALITY DISORDERS

A relatively wide range of dynamic therapies have been evaluated for a number of personality disorders, against both active and inactive control treatments. A number of small trials report intensive, relatively brief (25-40 sessions) PDT to be superior to minimal contact (166), waitlist (167,168) and treatment as usual (169-172). Some studies demonstrated the value of longer-term treatments for specific diagnoses, for example, borderline personality disorder (173,174).

Brief therapies do less well against active controls. In mixed personality disorder populations, manualized PDT was not superior to supportive psychotherapy (175), adaptive psychotherapy (167) or non-manualized community-delivered PDT (176). In a comparison of non-manualized PDT with CBT, the latter was more efficacious over a 20-session treatment and follow-up for avoidant personality disorder (168). In contrast, a trial of manualized PDT versus CBT for cluster C personality disorder patients reported no significant differences and a somewhat more rapid reduction of symptom distress in the PDT group (177). A further comparison between PDT, CBT and brief relational therapy (which focuses on ruptures in the therapeutic alliance) found that the latter two treatments were associated with a higher percentage of clinically significant and reliable change in the treatment of cluster C personality disorder, although the differences were not significant (178).

There have been larger trials with active treatment comparisons focused on borderline personality disorder. Transference-focused psychotherapy was shown to be superior to supportive psychotherapy and dialectical behaviour therapy on some symptom measures (improving irritability, anger and assault and impulsivity) (179) as well as a number of attachment-related measures (180). Similarly, mentalization-based treatment was shown to be superior to structured clinical management of equal intensity (181), particularly for patients with more than two personality disorder diagnoses (182). Mentalization-based treatment was also found to be superior to supportive group therapy, but only in terms of global assessment of functioning, at termination (183) and at 18-month follow-up (184). However, an RCT comparing transference-focused psychotherapy and CBT (schema-focused therapy) found CBT to be more effective, particularly because early dropout rates were higher for the former treatment (185). In this context, it is noteworthy that the introduction of mentalization-based treatment to a specialist unit for borderline personality disorder was historically associated with a substantial reduction of dropouts (from 15% to 2%) (186).

While the inclusion of general psychiatric management in a review of PDT may perhaps be controversial, this

"dynamically informed" intervention, manualized by two psychodynamic practitioners (187), owes much to dynamic techniques and conceptualization of borderline personality disorder. It has been shown to be comparable to dialectical behaviour therapy at termination (188) and 2-year follow-up (189).

Meta-analyses

There are few meta-analyses specific to PDT for personality disorders, although a number of the meta-analyses focusing on long-term psychotherapy capture many if not all of the relevant studies (190,191).

One meta-analysis of controlled and uncontrolled studies for patients with comorbid depression reported large pre-post effect sizes (d=1-1.27) and superiority to waitlist, but no significant differences in efficacy compared to other treatments (63). The most comprehensive meta-analysis reported medium effect sizes compared to inactive controls (31). Active treatment comparisons yield insignificant but negative effect sizes (g=−0.15, 95% CI: −0.3 to 0.1) and no significant difference at follow-up.

Breaking down outcomes to symptomatology, global functioning, interpersonal problems, depression and suicidality also revealed no significant differences between PDT and other therapies on any of these dimensions, but medium effect sizes in relation to control treatments. A marginally significant association between the number of sessions and effect size is reported.

However, it would be wrong to argue that complex disorders always require complex and long-term PDT interventions. Patients with chronic mental disorders (average 5-year chronicity), who were frequent utilizers of mental health services, were randomized to treatment as usual or very brief (8-session) PDT (192). Six months post-treatment there were significant benefits in terms of general psychiatric distress, social functioning, quality of life, and resource utilization in terms of outpatient attendance, general practitioner contacts, nurse contacts and medication. The cost of psychotherapy was recouped through reductions in resource use. The study underscores the absence of a simple linear relationship between the length of a dynamic treatment and the severity of psychopathology.

Comment

The evidence concerning personality disorders is relatively robust in highlighting the superiority of PDT over controls across key clinical variables including suicidality, global and interpersonal functioning, as well as comorbid psychopathology.

The American Psychological Association (Division 12) has designated transference-focused psychotherapy a well-established treatment for borderline personality disorder, while mentalization-based treatment is deemed probably efficacious. In fact, a number of the comparator treatments considered above also have strong claims to being empirically supported, notably relational psychotherapy for general personality disorder (193), manualized dynamic supportive therapy (194) and brief adaptive psychotherapy (195).

A review of the treatment of personality disorders (196) summarizes the characteristics required for an effective treatment as structured, focused on developing agency, integrative of feelings and actions, active and validating, and incorporating supervision. Most dynamic therapies will incorporate these features. Their relative efficacy is thus hardly surprising.

DISCUSSION

What can be concluded about the efficacy of PDT? Intriguingly, different reviews of the same literature appear sometimes to reach dramatically different conclusions (190, 191,197-201). There is a clear need for authors to declare interests, since the conclusions of reviews often appear to reflect the authors' theoretical orientation, just as the outcomes of individual studies appear to be highly correlated with the first author's affiliation (202). This tendency is regrettable, because the lack of balance and the determination to use statistics primarily for support leads to entrenched traditions and conflicts with the need to innovate through the process of collaboration that is so characteristic of discovery science.

The extension of the evidence-based movement to psychotherapy, which we strongly support, may have reinforced a conservatism by raising the bar for accepting innovative approaches. Could CBT be discovered and disseminated now under the empirically supported therapies paradigm (203)? Complex combinations of techniques have been packaged as empirically supported therapies. Increasingly, developers have prioritized the implementation of packages without regard to the unique value of each component. These treatment packages evolve in relation to what many now consider a less-than-adequate system of diagnostic classification (204-206). Transdiagnostic considerations will ultimately outweigh syndrome-specific treatment recommendations.

Given all this, is it possible to make meaningful recommendations about PDT based on the evidence? The following suggestions seem to be well grounded in data:

- Treatment approaches generated from PDT principles appear to benefit individuals who present with depression, some forms of anxiety, eating disorders and somatic problems.
- Implementations of the same principles in long-term treatments (1 year and longer) appear to benefit individuals with complex disorders where the severity manifests as a combination of syndromal and spectral-level problems (a generally high level of vulnerability to psychopathology) (207,208).

- There is little evidence to suggest that PDT is superior to other therapeutic approaches. Its implementation in most instances will depend on the availability of appropriately trained personnel and their willingness to acquire the specific techniques that have been shown to be efficacious to a level of competence on a par with personnel delivering treatments in RCTs.
- The speed of recovery and cost-effectiveness of interventions is a crucial parameter, since there is little evidence that in the long term major differences exist between therapies in terms of recovery or remission. Any apparent superiority of long-term PDT is attributable to the prolonged contact between patient and therapist.

Looking towards the future, the modularization of interventions and their combination to meet the needs of individual patients is the highest priority. Currently, there are very few systematic, empirically tested protocols for combining treatments in either pharmacotherapy or psychotherapy. Yet, the reality is that most patients receive empirically untested combinations. In the newly established self-report system of the U.K.'s Children and Young People's Improving Access to Psychological Therapies programme (CYP IAPT), the treatment most commonly offered – almost twice as often as anything else – is "other"; that is, not CBT, family therapy, PDT or counselling.

In developing new therapies, researchers have to aim to innovate in the direction of directly addressing the deficits patients with mental disorder present with. The alignment of PDT with such deficits is the most important priority. We may well be concerned that current PDT approaches are too deeply rooted in the technical preferences of developers (supportive vs. expressive, relational vs. ego-oriented, self-psychological vs. conflict-focused, etc.). This is the language of professionals rather than patients. Each approach may have meaningful components in relation to particular individuals, but how is a therapist to know which approach to apply to whom? The evidence certainly does not speak to such a choice.

If the field is to advance, we have to do more than talk about the global effectiveness of a heterogeneous category of approaches, such as PDT, in relation to a heterogeneous group of patients, such as those who experience depression. There have been some attempts to match particular presentations to specific PDT techniques (e.g., work on introjective vs. anaclitic depression) (209-211). However, there is considerably more to be achieved by "playful" experimentation, probably driven by advances in bioscience and computational psychiatry.

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The NIMH Experimental Medicine Initiative

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Much has been written about the dire state of treatment development for mental disorders (1). While there has been progress in the development of devices and psychosocial treatments, psychopharmacology over the past decade appears to have stalled after four decades of exuberant growth (2).

There are several reasons for the lack of progress in medication development: preclinical studies appear neither predictive or reproducible, there are few novel targets for Phase I and Phase II studies, and several expensive recent Phase III studies have failed. Psychiatric drug development is now seen as high risk. Indeed, large pharmaceutical companies have reduced investment in central nervous system disorders from 267 projects in 2009 to 129 projects last year, with many of these projects focusing on neurological and not psychiatric disorders (3).

It is important to note that four decades of drug development resulting in over 20 antipsychotics and over 30 antidepressants have not demonstrably reduced the morbidity or mortality of mental disorders. While there may be many explanations for the unabated public health needs associated with mental illness, there can be little doubt that we need additional research and development to provide the preventive interventions and cures that will reduce morbidity and mortality. Current medications have an important role in the toolbox of interventions but, either alone or in combination with other treatments, they have not proven sufficient. The question is how to develop the next generation of interventions.

PREVIOUS CLINICAL TRIALS

The National Institute of Mental Health (NIMH) has tried to answer this question by focusing on each of the issues noted above: problematic preclinical studies, lack of novel targets, and failure of Phase III trials. Others have argued for the need to move rapidly into human trials due to the difficulty extrapolating from preclinical results (4,5). Here we describe changes in the clinical trials portfolio to search for novel targets and increase the likelihood of Phase III success. The approach has been called the shift to experimental medicine at NIMH. Although this term has been used to describe broadly the clinical study of mechanisms of disease, for NIMH, experimental medicine refers to an approach to clinical trials.

The first step before changing the clinical trials approach was a review of the portfolio in 2012. In the previous year, NIMH supported over 250 clinical trials at a cost of roughly $150M per year. More than half of these trials were for psychosocial interventions. Our initial review demonstrated a large number of under-powered trials that were slow to recruit and even slower to publish. Indeed, a 2012 review of trials across the National Institutes of Health (NIH) reported that fewer than half published results within 30 months of completion (6). Most trials were looking for an efficacy signal, but were designed not to rigorously test a hypothesis about how or for whom the intervention should work. Few trials included any test of mechanism of action. Trials rarely included measures of dose-response or tests of duration that could inform their adoption and reimbursement in the real world. Given the range of issues, NIMH announced in 2014 that it would no longer accept proposals for clinical trials unless they were responsive to a Request for Applications (RFA).

NEW CLINICAL TRIALS

In 2014, NIMH released three RFAs to solicit proposals for clinical trials (see http://grants.nih.gov/grants/guide/rfa-files/). In line with an experimental medicine approach, each of these RFAs refocused trials from simple tests of efficacy to studies of disease mechanism (7). The new approach required a measure of target engagement, where the target ideally was linked to some mechanism of disease but could also be a mechanism of action of the intervention. The prototype of a target might be a measure of receptor occupancy. A clinical trial of a drug thought to work as a dopamine receptor antagonist would need to demonstrate a dose for engagement or occupancy of the dopamine receptor and then test for efficacy at that dose.

This simple requirement has two important implications. First, it allows negative efficacy data to be informative. Second, it allows a test of the importance of the target. In five decades of treatment development, there have been essentially no mechanisms falsified in neuropharmacology, in part because target mechanisms are rarely tested in clinical trials.

Of course, receptor occupancy is a high bar for target engagement, unlikely to be feasible in most studies. For psychosocial studies, the target could be a shift in attentional bias or social cognition or family dynamics, as assessed by changes in objective measures included in the trial. For device studies, the target might be a change in EEG or evoked potentials or the blood-oxygen-level dependent (BOLD) signal. The choice of target is critical because the choice of intervention is almost always iterative. Each new intervention is a step along a path toward much more

effective treatments. To accelerate that path, NIMH believes that an understanding of the target will prove to be the critical insight, not a slight increase in effect size.

As a further test of this approach, NIMH sponsored a series of contract trials called Fast-Fail trials (FAST). These trials were based on an analysis of failed Phase III trials that suggested a need to insert go - no go decisions into earlier phases of the development process (5). By failing early and often, development could focus on the treatments most likely to succeed in Phase III. In addition to requiring measures of target engagement, the FAST studies had specific milestones built in for assessing progress. Since these trials were funded as contracts, project management was rigorous and funding was contingent on hitting these milestones. Current trials include assessing the kappa opiate receptor for anhedonia in depression and a GABA-A agonist for social cognition in autism, with measures of target engagement and specific efficacy outcomes built in.

ENHANCING IMPACT

The new experimental medicine approach asks applicants to answer two simple questions about their experimental design: Will negative results be informative? Will positive results have an impact? Target engagement addresses the question about negative results. The impact of positive results is more complicated. In spite of the considerable experimental evidence of efficacy for targeted psychotherapies such as cognitive behavioral therapy and dialectical behavior therapy, and considerable data about the most effective use of medications, our field faces a crisis of failed implementation.

There are at least three issues affecting implementation. First, in most communities, in both the developed and the developing world, there are too few clinicians with supervised training in either psychopharmacology or those psychotherapies with the most evidence for efficacy. Second, for psychosocial treatments, the research establishing evidence rarely demonstrates the requisite dose or duration of treatment. And finally there has been little adherence to standards for fidelity, especially for psychotherapies. Without the regulatory framework that exists for medications and devices, neither patients nor payers know how to judge what a therapist actually delivers. Experimental medicine may not solve all of these issues, but properly designed experiments can at least establish dose and duration, with the potential for creating measures of fidelity as well.

BEYOND EXPERIMENTAL DESIGN

The aforementioned portfolio analysis revealed serious problems with several key measures of performance. While not ubiquitous, there were many trials that had failed to register in ClinicalTrials.gov, some with prolonged delays in enrolling the first subjects, and many failing to meet recruitment milestones. As noted above, many NIH trials were also slow to publish following completion of the study, with as many as 30% failing to publish any results (6). NIMH has also altered its expectations for clinical trials beyond experimental design. All trials funded by NIMH must be registered in ClinicalTrials.gov. To expedite enrollment, all multi-site trials are expected to have a centralized institutional review board (IRB). Recruitment will now be tracked in all studies, with funding terminated for studies that persistently fail to meet recruitment goals.

NIMH-funded clinical trials are now required to submit individual level data on a quarterly basis to the National Database for Clinical Trials Related to Mental Illness (http://ndct.nimh.nih.gov). The importance of sharing individual-level data became apparent in a recent reanalysis of 37 published clinical trials (8). In 35% of the trials, the reanalysis led to a different interpretation than reported in the original paper, with implications for the types and numbers of patients who should be treated.

Two other issues deserve note. Clinical trials of mental disorders have been impaired by the heterogeneity of our diagnostic classifications. It is not hyperbole to suggest that a study of a new drug for major depressive disorder is analogous to giving a new antibiotic to everyone with fever. No one should be surprised that 30% of patients respond to placebo and 50% fail to respond to the new treatment. We need precision medicine for mental disorders. The Research Domain Criteria (RDoC) project seeks to go beyond symptom-level classification to identify more precise categories that could be used to stratify patients for clinical trials (9). This approach may also yield new clinical targets, such as anhedonia, fear reactivity, or aspects of executive function, that take us beyond the current focus on antidepressants, antipsychotics, and anxiolytics.

Finally, it is a curious paradox that nearly all clinical trials study a single intervention and yet in the real world of practice nearly all patients receive multiple interventions. While research demands the purity of single variables, we must find a way for science to align more closely with the practical needs of patients. Is it realistic to expect conditions as complex as psychotic, mood, or anxiety disorders to respond to a singular intervention? The treatment of diabetes now involves a package of psychosocial, medical, and device based interventions. Surely the time has come to recognize that there is not a magic bullet for most people with mental disorders, that the best treatment will involve access to multiple interventions tailored to the needs of an individual patient and selected by an informed patient working with an informed provider. The NIMH supported Recovery After Initial Schizophrenia Episode (RAISE) study is an example of this approach that could serve as a model for future trials (see http://www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml).

The shift to deployment focused intervention studies, which take "real world" issues into account, may ostensibly appear to be a challenge to an experimental medicine approach.

In fact, it is essential for understanding both targets and impact.

CONCLUSIONS

We need a next generation of treatments for mental disorders. As one step towards this goal, NIMH has introduced a new set of requirements for clinical trials. The design of these trials follows an experimental medicine approach, with a focus on target engagement. Beyond design, these trials will require new levels of transparency and efficiency.

Public health success will ultimately depend on more precise stratification of patients for trials and the development of combinations of treatments that can optimize outcomes.

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The human connectome in health and psychopathology

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A basic tenet of biological psychiatry is that psychiatric disorders are driven by abnormalities in brain function, which in turn reflect abnormalities in the underlying brain circuits, i.e., in the wiring of the brain. These circuit abnormalities presumably reflect a complex interplay between genes and environment. Many psychiatric disorders have strong genetic underpinnings: common or rare variants of genes, individually or in combination, elevate the susceptibility to disorders such as autism (1), schizophrenia (2), and many others.

Most psychiatric disorders are thought to be neurodevelopmental in nature, either because symptoms typically arise during childhood (e.g., autism) or because the interactions between genes and environment begin early, even if the onset of the disorder becomes evident only in adolescence or adulthood.

To better understand, diagnose, and treat psychiatric disorders, it is crucial to obtain deeper insights into brain circuits in health and disease and in humans and animal models. Here, we focus on the relevance of human *in vivo* neuroimaging, particularly involving magnetic resonance imaging (MRI). We briefly address three major points. First, recent neuroimaging studies have already provided important insights about abnormalities related to brain structure, function, and connectivity in psychopathology. Second, recent advances in neuroimaging of healthy adults, including many driven by the Human Connectome Project, offer exciting prospects for accelerated progress in characterizing disease-related brain connectivity abnormalities. Third, methodological limitations of each neuroimaging method, some of which are inadequately appreciated, require critical assessments and careful interpretation of research findings, especially when placed in the context of the extraordinary complexity of brain circuits revealed by studies of laboratory animals.

MEASURING HUMAN BRAIN STRUCTURE, FUNCTION, AND CONNECTIVITY

The human brain contains about 90 billion neurons and 150 trillion synapses. Physically, the dominant structure is the cerebral cortex, a highly convoluted sheet containing most of the synapses but only ~20% of the neurons (3). The cortex is a mosaic containing hundreds of distinct areas (parcels), but accurate mapping of their location, function, and connectivity is an ongoing quest.

Individual variability in cortical structure, function, and connectivity is likely to underlie much of what determines our unique personalities, including behavioral disorders. However, cortical interactions with a complex array of subcortical nuclei (~8% of brain volume but only ~1% of neuronal number) and with the cerebellum (~10% of brain volume, ~80% of the neurons) are extremely important as well (3,4). Data from nonhuman primate studies suggest that there are ~10,000 long-distance pathways between cortical and subcortical parcels ranging widely in their connection strength (5,6). Deciphering even a modest fraction of this circuitry in the human brain is truly a daunting endeavor.

Four major MRI modalities provide views of human brain structure, function, and connectivity. First, structural MRI uses volume-based analyses to estimate the distribution of gray matter regions, and surface-based analyses to assess cortical thickness and folding patterns. Second, task functional MRI (fMRI) identifies regions of increased or decreased fMRI blood oxygen level dependent (BOLD) signal that in turn reflects brain activity (synaptic currents and neuronal spiking) via a complex and still poorly understood mechanism of neurovascular coupling (7). Third, diffusion imaging (dMRI) and tractography enable characterization of "structural connectivity" using preferential diffusion of water molecules along the length of axons to estimate the dominant fiber orientation(s) in each white matter voxel, then inferring long-distance connectivity based on (deterministic or probabilistic) tractography algorithms. Tractography is conceptually the closest approach to inferring direct anatomical connectivity, but it has significant practical limitations owing to the prevalence of crossing fibers, branching fibers, and other methodological confounds that can give rise to false positives and false negatives (6). Fourth, resting-state fMRI (rfMRI) relies on correlated fluctuations in the BOLD signal to infer "functional connectivity", that typically reflects brain regions sharing a history of coactivation. This may reflect anatomically direct connectivity, but coactivation may occur instead or in addition through common inputs or indirect connections (8).

The spatial resolution of each MRI modality depends on the size of individual volume elements ("voxels"), which in turn reflects the signal to noise constraints of each approach. Voxel dimensions are typically 1 mm for structural MRI, ~3 mm for fMRI, and ~2 mm for dMRI, but methodological advances by the Human Connectome Project described below have substantially reduced voxel sizes for each mo-

dality. In the remainder of this paper, we focus mainly on advances revealed by analyses of structural and functional connectivity.

BRAIN CONNECTIVITY IN PSYCHIATRIC DISORDERS: RECENT HIGHLIGHTS

The past decade has seen a burgeoning literature applying currently available methods for assessing functional and structural connectivity to our understanding of course, outcome, treatment response and heterogeneity in psychiatric disorders, as well as their developmental antecedents (9). In many ways these studies are still in their infancy, but here we describe a few examples that highlight the potential utility and power of these methods for helping us to understand the pathophysiology of a range of psychiatric disorders.

Not surprisingly, one major focus has been to assess whether individuals with various forms of psychiatric disorders differ from individuals without psychiatric disorders in either structural and/or functional connectivity. For example, a recent meta-analysis of obsessive-compulsive disorder indicates that this illness is associated with altered structural connectivity between lateral prefrontal and parietal regions (10).

Importantly, the field is now moving beyond basic comparisons to healthy individuals by using measures of functional and structural connectivity to elucidate the progression of brain changes across different stages or phases of illness (11), and between individuals who have putatively different psychiatric disorders (12,13). This offers the prospect of critical insights about potentially dissociable etiological pathways.

A growing number of investigators are examining the relationship between individual differences in specific symptom or cognitive domains and structural and functional brain connectivity, both within and across diagnostic categories (14,15). This aligns well with the Research Domain Criteria (RDoC) initiative (16,17), which focuses on identifying core brain-behavior systems that may be critical for understanding psychopathology.

Another important thrust is to use connectivity measures to understand the predictors and mechanisms of treatment response for psychiatric disorders (18,19), providing insights into both the types of individual difference characteristics and the types of treatments that may facilitate plasticity.

Finally, an exciting new direction is to use structural and functional connectivity measures to elucidate risk factors for and the developmental antecedents of psychiatric disorders (20-22). Such information may provide novel avenues for early intervention or even prevention, as well as clues as to pathophysiology.

THE HUMAN CONNECTOME PROJECT AND BEYOND

The efforts summarized above are starting to provide valuable insights into circuit-based mechanisms of psychiatric disorders, but they represent only the tip of an "information iceberg" that can be better exposed using improved neuroimaging methods. Like many other arenas of neuroscience, neuroimaging has benefited from many recent improvements in data acquisition and analysis that hold promise for advancing our understanding of circuit level dysfunction in psychopathology. Here, we illustrate a few of the advances in human neuroimaging enabled by the Human Connectome Project (23).

Among the many improvements in data acquisition, the two most significant are "multi-band" pulse sequences, which benefit both fMRI and dMRI data acquisition (24,25), and customized scanners with increased maximum gradient strength, which benefits dMRI (24,26). For fMRI, this translates to better resolution in space (2 mm vs. typical ~3 mm voxels; 1.6 mm voxels at 7 Tesla), which enables accurate mapping of data to the cortical ribbon, and in time (0.7 s vs. typical ~2 s for each frame, or image volume), which increases sensitivity to dynamic activity patterns and also helps filter out noise. For dMRI, the improvement is in spatial resolution (1.25 mm vs. typical ~2 mm), which enables better identification of crossing fibers (27), plus the prospect of dealing better with gyral biases (6). Nonetheless, even with improved resolution, given the known densities of neurons and synapses, a fMRI voxel in the Human Connectome Project contains ~250,000 neurons and ~250,000,000 synapses, while a dMRI voxel contains hundreds of thousands of axons. Hence, the gulf between the micro- and macro-connectome domains remains enormous.

Improvements in Human Connectome Project data analysis include concurrent use of appropriate geometric models for cerebral cortex (as a surface mesh) and subcortical structures (as voxels) (28), and improved intersubject alignment using functionally relevant features as well as folding patterns (29). This is critical, given the dramatic individual differences in the physical pattern of cortical convolutions and the variability in size and location of cortical areas relative to folds.

The Human Connectome Project expects to complete data acquisition on 1200 healthy adult twins and nontwin siblings in 2015. Results from the ~500 subjects released to date are already beginning to emerge. The Connectome DB database serves as a user-friendly workhorse platform (http://www.humanconnectome.org) that to date has enabled sharing of nearly a petabyte (1 million gigabytes) of data with the scientific community. For rfMRI, this includes extensively processed data such as parcellations based on functional connectivity and functional connectivity matrices for individuals as well as population averages.

In 2014, the National Institutes of Health announced a Connectomes Related to Human Disease funding opportunity (http://grants.nih.gov/grants/guide/pa-files/PAR-14-281.html) for the study of brain disorders using advanced methods of data acquisition and analysis, with the resultant data to be shared via a Connectome Coordinating Facility that is an extension of Connectome DB. Hopefully, this

promotion of common strategies of acquiring and sharing high-quality neuroimaging data will accelerate progress in characterizing circuit abnormalities.

CONCLUSIONS

While there is reason to be optimistic about continued advances, it is also vital to be realistic about the limits that are attainable using current technologies. Ideally, we would like to see methods that enable diagnosis at the level of individual subjects. Further, it will be increasingly critical in future work to synergistically integrate analyses of both functional and structural connectivity, given their complementary strengths and information content.

In addition, it will be important to appreciate relationships in connectivity across spatial scales, such as understanding how disruption of local circuits (i.e., excitation/inhibition imbalance) may influence both larger scale functional connectivity (29), and even potentially structural connectivity over time.

The degree to which these aspirations will be feasible remains open to question, but we believe that the advances afforded by endeavors such as the Human Connectome Project and related projects are helping to provide the tools and data that are vital for accelerating progress.

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What has serotonin to do with depression?

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The "serotonin hypothesis" of clinical depression is almost 50 years old. At its simplest, the hypothesis proposes that diminished activity of serotonin pathways plays a causal role in the pathophysiology of depression. This notion was based on the depressogenic effects of amine depleting agents such as reserpine, as well as the actions of antidepressant drugs such as monoamine oxidase inhibitors and tricyclic antidepressants, discovered by clinical serendipity, but later found in animal experimental studies to potentiate the effects of serotonin and other monoamines at the synapse (1).

This pattern of theory making – moving from the pharmacological actions of drugs with some efficacy in treatment to biochemical notions of causation – has been common in biological psychiatry. In such an undeveloped field this approach, though logically precarious, has been a useful heuristic and, in the case of the dopamine hypothesis of psychosis, has been strikingly upheld by advanced brain imaging techniques (2). However, the serotonin hypothesis of depression has not been clearly substantiated. Indeed, dogged by unreliable clinical biochemical findings and the difficulty of relating changes in serotonin activity to mood state, the serotonin hypothesis eventually achieved "conspiracy theory" status, whose avowed purpose was to enable industry to market selective serotonin reuptake inhibitors (SSRIs) to a gullible public (3).

IS SEROTONIN STILL RELEVANT TO AN UNDERSTANDING OF DEPRESSION?

In biological psychiatry, pathophysiological hypotheses are not easily refuted. More often they simply seem to become irrelevant as new models of causation take their place. In an era of neural networks and systems level neuroscience, "single" neurotransmitter theories of depression look increasingly implausible. Is serotonin still worth thinking about in relation to depression?

The best evidence that serotonin plays a role in the pathophysiology of depression comes from studies of "tryptophan depletion", where an acute dietary manipulation is employed to produce a transient lowering in brain serotonin activity through diminishing availability of its precursor amino acid, tryptophan. In healthy participants with no risk factors for depression, tryptophan depletion does not produce clinically significant changes in mood; however, recovered depressed patients free of medication can show brief, clinically relevant, depressive symptomatology (4). Interestingly, the same is true of recovered depressed patients undergoing catecholamine depletion with alpha-methyl-para-tyrosine (5).

Overall, this evidence suggests that impairing serotonin function can cause clinical depression in some circumstances, but is neither necessary nor sufficient. In addition, the depressogenic effects of tryptophan depletion are much more apparent in people who have experienced prior episodes of depression than in those simply at high risk of illness, for example by virtue of a strong family history (6). This suggests that low serotonin function may compromise mechanisms involved in maintaining recovery from depression rather than having a primary effect to lower mood in all vulnerable people.

These findings also hint at a role for diminished tryptophan availability in triggering depression, particularly in people with a previous history of illness. Interestingly, lower plasma levels of tryptophan are one of the few reasonably robust findings in patients with more severe forms of depression (7) and, more recently, have been linked to peripheral inflammation and consequent induction of the tryptophan metabolizing enzyme indoleamine 2,3-dioxygenase (8). Inflammation could therefore produce depression in vulnerable individuals by lowering plasma tryptophan and diminishing brain serotonin activity. Conceivably, such an effect could explain the diminished efficacy of SSRIs in depressed patients with high levels of inflammatory biomarkers (9).

SEROTONIN AND ANTIDEPRESSANT ACTION

Undoubtedly, a major reason for the continuing interest in serotonin and depression is the fact that SSRIs are useful antidepressant drugs for some patients. Elegant basic studies have revealed intriguing molecular and cellular consequences of repeated SSRI administration in animals, for example increases in hippocampal cell proliferation and enhanced expression of neuroplasticity related proteins such as brain derived neurotrophic factor (BDNF) (10). However, linking such changes to resolution of the clinical depressive syndrome is challenging. More pertinent in this respect are neuropsychological studies which show that, in both healthy participants and depressed patients, administration of SSRIs leads to positive shifts in the way the brain appraises emotionally-valenced information. This effect occurs very early in treatment, prior to clinical antidepressant effects, and appears to be mediated via serotonergic innervation to limbic circuitry, particularly the amygdala (11).

This work gives a new insight into how serotonin pathways may influence mood in depressed patients, that is by altering the way the brain appraises emotionally-laden information at an implicit level. Unlike mood, emotions are

relatively short-lived, automatic responses to internal or external stimuli, and in depressed patients emotional responses are reliably negatively biased (12). Thus, from this viewpoint, increasing serotonin activity in depressed people does not influence subjective mood directly but, rather, as a secondary consequence of positive shifts in automatic emotional responses.

Over time, it is suggested, this positive biasing of automatic processing would, in an appropriate interpersonal environment, lead to changes in the strategic processing associated with conscious emotional experience. This psychological process is likely to involve re-learning a range of emotional associations, which might account for the gradual onset of clinical antidepressant activity (11). In addition, the notion that "re-learning" is involved in subjective improvement in depression sits well with the finding noted above that antidepressants such as SSRIs promote synaptic plasticity, an effect classically associated with learning (13).

COMPUTATIONAL APPROACHES TO SEROTONIN FUNCTION

Computational neuroscience offers a framework that allows the role of specific neurotransmitters to be dissected from within a complex, interconnected and dynamic system such as the brain. The paradigmatic example of a computational approach to understanding the function of a central neurotransmitter is the finding that activity in a subset of dopaminergic neurons, projecting from the ventral tegmentum throughout the brain, sharply increases when an unexpected reward occurs (14). Computational accounts suggest that these dopamine neurons contain information about the "reward prediction error", which is calculated simply as the difference between the reward the animal "expected" to receive and what it actually received (15). This provides a compelling quantitative account of the role of dopaminergic neurons in updating beliefs about the environment.

The role of serotonin in cognition has not, to date, been characterized as successfully as the dopaminergic reward prediction error signal. This may in part be due to the technical challenges of identifying serotonergic neurons electrophysiologically or the low concentrations of serotonin compared to dopamine in the central nervous system, problems which may be more readily circumvented in the future by advances in optogenetics (16). Whatever the cause, no existing computational account of serotonergic function commands the empirical support enjoyed by the dopaminergic model.

As a result, before reviewing the specific proposed models of serotonergic function, it is useful to consider the broad type of information that the serotonergic system *could* transmit, given its gross anatomy and neurochemistry. Serotonergic neurons, in keeping with other central monoaminergic neurotransmitters such as noradrenaline and dopamine, project from small central nuclei throughout much of the rest of the central nervous system. This anatomical layout is ideal for broadcasting relatively simple messages which are of general interest to many different regions of the brain, such as the reward prediction error signal carried by dopamine. This is not to say that the serotonergic system has a limit of only one kind of signal; there may be some anatomical specificity in the information transmitted, and the complex range of serotonergic receptors allows for signals to be multiplexed even in neurons projecting to the same region (17).

Current models of serotonergic function have tried to account for three broad observations about the effects of enhancing serotonergic function in animals and humans: first, that it influences response to aversive stimuli; second, that it increases behavioural inhibition; and third, that it improves the symptoms of depression (18).

An initial computational account of serotonergic transmission suggested that it acted in opponency to dopamine, transmitting a "punishment prediction error". That is, phasic serotonergic activity reports when events were worse than expected (19). This model is able to account for the effect of serotonergic modification on behavioural responses to stress and threat, as it suggests that serotonin broadcasts crucial information for learning about aversive outcomes. An elaboration of the model suggests that, in addition to the *phasic* punishment prediction error signal, *tonic* serotonergic activity represents the average, or expected frequency of punishments (20). This links the effect of serotonin on aversive processing to behavioural inhibition, as the more frequently punishments are expected to occur when actions are taken, the more advantageous does a cautious approach to action become.

A second variant of this model frames the role of serotonin as controlling "delay-discounting", which describes the observation that an immediate reward (say, being given a bar of chocolate now) is generally valued to a greater extent than a delayed reward (being given a bar of chocolate in a week's time). Computationally, this effect can be described by representing the value of a reward numerically (a bar of chocolate could have an immediate reward value of 100) and then systematically reducing this value as a function of how long a delay there is until it is received (the value of the same chocolate bar to be eaten in a week's time may be 50) (21). Serotonin has been suggested to control how "steep" this discounting process is – specifically, high levels of serotonin make the process flatter and thus reduce the difference between immediate and distant rewards (22,23). Flattening the discount rate in this manner makes it more likely that the animal will be willing to wait for a delayed reward, and explains why enhancing serotonergic function reduces impulsive behaviour.

A third computational model, developed by Dayan and Huys (18), may be more relevant to the role of serotonin in depression and its treatment. Here, serotonin is perceived as influencing the way that one thought leads to another, specifically by inhibiting chains of thoughts predicted to lead to negative affective states ("let's not go there"). From this

viewpoint, the role of serotonin is to ensure that thoughts with potentially negative emotional consequences are relatively underexplored; hence facilitation of serotonin produces a bias towards optimistic valuations, as rewarding thoughts are "visited" more frequently than punishing thoughts. This is consistent with actions of SSRIs on emotional processing described earlier (11). Conversely, tryptophan depletion would be expected to undermine this effect of serotonin, leading to greater access to negative thinking patterns. In an individual where particularly bleak patterns of negative thoughts have been established during previous depressive episodes, tryptophan depletion could result in such experiences being readily re-accessed, leading to the return of clinically significant depressive symptoms.

CONCLUSIONS

Simple biochemical theories that link low levels of serotonin with depressed mood are no longer tenable. However, experimental and computational accounts of how serotonin influences emotional processing throw an intriguing light on the neuropsychology of depression and its pharmacological treatment.

Whether this information can be harnessed to predict therapeutic response to SSRI treatment at an individual level is an important topic for clinical translation.

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The interaction between stress and genetic factors in the etiopathogenesis of depression

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The presence of a genetic component to depression has been established by family, twin and, to a lesser extent, adoption studies. Family studies have shown that first-degree relatives of patients with depression have on average three times the risk of depression of those without a family history of the disorder (1), but at least one study of clinically ascertained narrowly defined depression estimated the risk in siblings to be nearly ten times the risk in controls' siblings (2). A systematic meta-analysis including data from five twin studies reported an average heritability estimate of 37% (1), but a clinically based twin study provided an estimate of over 70% (3).

Genetic association studies have mainly focused on neurotransmitter and hypothalamic-pituitary-adrenal (HPA) axis related genes (4,5). Although almost 200 genes have been investigated through this type of "candidate gene" approach, only a few findings have been replicated (6), with seven candidate genes explored by meta-analysis yielding statistically significant results (5HTTLPR, APOE, DRD4, GNB3, HTR1A, MTHFR and SLC6A3) (6).

Since a landmark publication in 2007 of a genome-wide association study (GWAS) of seven common diseases, one of which was bipolar disorder (7), association studies of major depression have also taken a GWAS approach. Unfortunately this has been less successful so far than in other common psychiatric disorders, including Alzheimer's disease, bipolar disorder and schizophrenia. A recent mega-analysis conducted on eight GWAS included 18,759 unrelated individuals (9,240 major depressive cases and 9,519 controls) and analyzed more than 1.2 million single nucleotide polymorphisms (SNPs). No SNPs achieved the stringent criteria that have now become the standard for declaring genome-wide significance ($p < 5\times10^{-8}$) (8).

Thus, despite substantial heritability, there has been a failure to robustly identify genetic variants that contribute to depression. Plausible explanations include heterogeneity (diagnostic, etiological or both), the existence of multiple tiny genetic effects that require even larger samples, and failure to take into account gene interplay with environmental factors.

The association between stress and depression is strong and compelling, with consistent evidence that life stressors influence the onset and clinical course of depression (9). On the other hand, not everyone who experiences such events develops the disorder and not everyone who becomes depressed appears to have a precipitating life event.

Methodological issues regarding stress assessment have been repeatedly discussed. First, there is the question of using a time consuming standardized interview versus a quicker checklist method. Research has consistently confirmed that semi-structured interviews are more accurate and effective than simple questionnaires (10). Second, there is the problem of direction of causality: is the subject's mental state influencing the event (or how it is reported) or is the event really precipitating depression? Researchers have tried to tease out events that are truly independent of the patients' own actions and mental state. Acute life events have been most consistently found to precede the onset of a depressive episode compared with chronic and distal events (11), but early life stress, specifically adverse childhood experiences (emotional, physical or sexual) have been shown to increase the risk of depression in adulthood and even in old age (12,13). Indeed, life events occurring long before the onset of depression have little or no relationship with adult depression once childhood maltreatment is controlled for (14).

One of the first attempts to study the effects of life events within a familial context used a semi-structured interview, the Life Events and Difficulties Schedule (LEDS) (9), and resulted in the provocative finding that not only did the relatives of depressed subjects have an increased rate of depression, but also they appeared to have an elevated rate of threatening events (15). Subsequent work with twins suggested that there is actually a modest but significant heritable component to self-reported life events (16) and a genetic correlation between self-reported life events and depressive symptoms in adolescents (17). However, this genetic effect is probably only characteristic of self-reported life events assessed by a questionnaire, since parental reports of life events occurring in the same adolescents showed no evidence of heritability. Furthermore, the phenomenon of familiarity of LEDS-detected threatening life events in relatives of depressed patients was shown to be explained by shared events, for example illness in a parent affecting both members of a sibling pair (2). This whole question of how life events are detected and defined has recently attracted renewed interest in the context of studies of gene-environment interaction.

Gene-by-environment interaction (GxE) studies aim to detect whether there are genetic influences affecting individual differences in response to the environment. The first GxE study of depression focusing on a specific genetic variant was reported by Caspi et al in 2003 (18). They found

that a functional polymorphism in the serotonin transporter linked polymorphic region (5-HTTLPR) moderates the effect of environmental factors (childhood maltreatment and stressful life events) on the risk of depression. Individuals carrying one or two copies of the relatively low-expressing short allele (s) had a higher risk of depression after being exposed to stressful life events or childhood maltreatment than homozygous for the long allele (l) (18).

Subsequently, there have been more that fifty studies trying to replicate Caspi's findings, and the results have been somewhat contradictory (4,19), with two "negative" meta-analyses (20,21) receiving much attention. However, Uher and McGuffin (22) have noticed a significant systematic effect of how life events were assessed, with negative studies being the ones that used subjective self-report measures. The most recent and complete meta-analysis, including 54 studies, has found strong evidence that 5-HTTLPR does indeed moderate the relationship between depression and adversity, particularly childhood maltreatment and specific objectively measurable stressors (23).

There is also support from recent data that interactions with 5-HTTLPR are stronger amongst individuals with chronic or persistent forms of depression (14,24,25). A recent study has also confirmed the presence of an interaction between 5-HTTLPR and various forms of childhood maltreatment (26). Currently, an ambitious large scale meta-analysis is underway, attempting to provide a definitive exploration of adversity, depression and 5-HTTLPR and including data from 35 independent groups and at least 33,761 individuals (27).

There is also emergent work suggesting that the s allele of the 5-HTTLPR polymorphism may confer a differential sensitivity to the environment, which may be either beneficial or negative (28). For example, a study of preschool children indicated that homozygotes for the 5-HTTLPR s allele were more vulnerable to depression at high stressful live events exposure, but showed reduced rates of depression at low stressful events exposure, appearing to benefit from a better environment (29). Furthermore, there is preliminary evidence that children with anxiety or depression respond more positively to psychological treatments if they carry the 5-HTTLPR s allele (30).

5-HTTLPR has become a forerunner for a whole range GxE interaction studies in mood disorders that are focusing on other candidates (19,31). Furthermore, epigenetic modifications, specifically DNA methylation, have been found in genes involved in GxE interactions, suggesting that these interactions could be mediated by epigenetic mechanisms (19,32). Recent studies implicate epigenetic mechanisms as an important link between early life adversity and sensitivity to stressful life events in adulthood (33). There is also emerging evidence that such interactions are not limited to unipolar depression. For example, a functional variant in the gene encoding brain derived neurotrophic factor (BDNF) may moderate the effect of adversity preceding onset of episodes in patients with bipolar disorder (34).

Until now, GxE studies have focused on candidate genes and, although the genome wide genotyping technology has been available for a while, no gene-environment wide interaction studies (GEWIS) have been conducted in psychiatric disorders so far. GEWIS face two major challenges: the availability of environmental data and statistical power (19). The other major problem is that the largest analysis to date by the Psychiatric Genomics Consortium, including nearly 20,000 individuals, failed to find any genome-wide significant hit (8). Therefore, we can predict that extremely large samples will be needed to detect GxE interactions that withstand the statistical stringency needed in genome-wide studies. Nevertheless, such efforts are ongoing and one of the highly welcome benefits of the post-genomic era in psychiatric genetics is the now universal acceptance that real advances can only be made by consortia that apply global standards of both scientific method and practical collaborative spirit.

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Phenomenological and neurocognitive perspectives on delusions: a critical overview

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There is considerable overlap between phenomenological and neurocognitive perspectives on delusions. In this paper, we first review major phenomenological accounts of delusions, beginning with Jaspers' ideas regarding incomprehensibility, delusional mood, and disturbed "cogito" (basic, minimal, or core self-experience) in what he termed "delusion proper" in schizophrenia. Then we discuss later studies of decontextualization and delusional mood by Matussek, changes in self and world in delusion formation according to Conrad's notions of "apophany" and "anastrophe", and the implications of ontological transformations in the felt sense of reality in some delusions. Next we consider consistencies between: a) phenomenological models stressing minimal-self (ipseity) disturbance and hyperreflexivity in schizophrenia, and b) recent neurocognitive models of delusions emphasizing salience dysregulation and prediction error. We voice reservations about homogenizing tendencies in neurocognitive explanations of delusions (the "paranoia paradigm"), given experiential variations in states of delusion. In particular we consider shortcomings of assuming that delusions necessarily or always involve "mistaken beliefs" concerning objective facts about the world. Finally, we offer some suggestions regarding possible neurocognitive factors. Current models that stress hypersalience (banal stimuli experienced as strange) might benefit from considering the potential role of hyposalience in delusion formation. Hyposalience – associated with experiencing the strange as if it were banal, and perhaps with activation of the default mode network – may underlie a kind of delusional derealization and an "anything goes" attitude. Such an attitude would be conducive to delusion formation, yet differs significantly from the hypersalience emphasized in current neurocognitive theories.

Key words: Delusions, schizophrenia, phenomenological psychopathology, neurocognitive models, salience dysregulation, prediction error, self-disorder, delusional mood

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THE PHENOMENOLOGICAL APPROACH TO DELUSIONS

The phenomenological approach focuses on delusion as a *phenomenon*, on its subjective or lived dimension: *what it is like* to have a delusion. A crucial feature of phenomenological psychopathology is its emphasis on the *mode, manner*, or *form* of the experience in question (1,2). The content of an experience, and the supposedly erroneous nature of beliefs presumably asserted or assumed by the patient, are less important than *how* the delusional world seems to be experienced and what *sort* of reality or existence the patient might ascribe to it.

Heidegger (3) referred to the latter dimensions of existence as "ontological", and distinguished them from object-oriented (what he called "ontic") modes of understanding experience. Delusions often involve a mutation in the *ontological framework* of experience that can alter the overall sense of existence and the world, including changes in felt reality-status, time, space, and self-experience (4-7).

Phenomenology is acutely sensitive to the potential *variety* of orientations a "deluded" patient might have. Also, it stresses that delusions may defy ready comprehension or empathy by normal individuals, since they sometimes involve radical changes in grounding structures and assumptions of human experience. Schizophrenia patients are often aware of the difficulty of conveying their experiences and the likelihood of being misunderstood (8). D.P. Schreber, the schizophrenia patient (of a grandiose paranoid sort) who is perhaps the most famous delusional patient of all time, spoke of matters that "lack all analogies in human experience and which I appreciated directly only in part with my mind's eye" (9, p. 123). "To make myself at least somewhat comprehensible I shall have to speak much in images and similes, which may at times perhaps be only *approximately* correct" (9, p. 2).

Recognizing this diversity and this difficulty in communication and comprehension suggests the need for in-depth, qualitative exploration of the patient's experiences. This requires replacing typical structured interviews with semi-structured formats (10) capable of illuminating how behavioral signs and symptoms are reflective of "*alterations of the structures of experiencing*" (11, p. 546).

Jaspers and "delusion proper"

The formulation of delusions offered by K. Jaspers, the father of phenomenological psychopathology, set the agenda for much subsequent psychiatric theory and investigation. Unlike contemporary uses of the term, in which "delusion" applies to aberrant beliefs in schizophrenic, paranoid, manic, psychotically depressive, and organic conditions, Jaspers considered "delusion proper" or "primary delusion" (1, pp. 95,98) (also known as "true" delusion) to be characteristic of schizophrenia.

"True" delusions could, thought Jaspers, be distinguished from delusion-like ideas, because the latter could be understood within the context of underlying personality or as exaggerations of normal emotions and affects. True delusions – which involve conviction, cer-

tainty, imperviousness, and impossibility as (merely) associated features – require learning about "the primary experience traceable to the illness" (1, p. 96), of which the apparently incorrect judgment is a secondary product.

For Jaspers, primary or true delusion involves a direct and unmediated experience that is *un*-understandable in light of previous experiences or beliefs. It is rooted in some indescribable alteration of personality (in the sense of a structural basis for subjectivity) or mode of consciousness of the patient: "a transformation in [one's] total awareness of reality" (1, p. 95) that remains "largely incomprehensible… and beyond our understanding" (1, p. 98). This primarily distinguishes it from "normal belief", "overvalued idea", and "delusion-like idea" (the latter found in other "psychotic" conditions as well as in schizophrenia).

Most subsequent phenomenological investigations have followed Jaspers' lead by focusing on delusion in schizophrenia, especially on three types of global change that contribute to the distinctive "incomprehensibility": delusional mood; disturbance of basic, minimal, or core self; and certain alterations in the apparent reality-status of delusional beliefs.

Jaspers suggested that delusions and delusional perceptions often arise out of feelings of unidentified significance (12). Occurring most notably in schizophrenia, this psychological state involves feelings of strangeness and tension and of suggestive yet ineffable meaning: "perception is unaltered in itself but there is some change which envelops everything with a subtle, pervasive and strangely uncertain light" (1, p. 98). The second feature involves mutations of basic self-experience: "The individual, though he exists, is no longer able to feel he exists. Descartes' *cogito ergo sum* (I think therefore I am) may still be superficially cogitated but it is no longer a valid experience" (1, pp. 122,578; see also 13,14). The third feature of "delusion proper" (1, p. 95) or of schizophrenic "incomprehensibility" (less explicitly stated by Jaspers: see 1, pp. 95,99,105,106) concerns the experienced reality-status of the delusional beliefs or quasi-beliefs (i.e., the degree or kind of reality that the delusional world is experienced as having).

Delusions may help to make a kind of rational sense out of what would otherwise be felt as disturbing, and otherwise inexplicable, changes in the very foundations of the experiential world – i.e., out of the torturous sense of things seeming "just so" (disconcertingly specific or precise) or bristling with strange, cosmic, intentional significance (15, p. 61), or of the disconcerting experiences of losing one's sense of self or of living in a shared and objective world.

Among the many interesting phenomenologically-oriented theorists in Jaspers' wake who wrote on delusions (these include Minkowski, Binswanger, Ey, Rümke, among others (6,14,16)) are P. Matussek and K. Conrad, psychiatrists who brought phenomenology together with Gestalt psychology.

Matussek: decontextualization

Matussek described a "loosening of the natural perceptual context" (17, p. 90) that allows "individual perceptual components" to float free of standard anchoring in commonsense unities or scenes; this, in turn, opens the way to attributions of exaggerated or peculiar significance and a bringing-together of isolated elements into relationships of delusional meaning that may be kaleidoscopic but can become rigidified. The delusional significance is typically "experienced directly as inherent in the object" (17, p. 98), as if rooted in sensory perception.

Matussek describes a distinctive combination of passivity with activity. The patient experiences a rigid gaze, feeling "held captive" (17, p. 94) by the object or objects. Yet he also has an exaggerated "ability" to "focus his attention on such isolated details" (17, p. 93) and may indeed take "pleasure" in this "fixing [of] attention" (17, p. 94), thereby further transforming the perceptual field via a "prolonged gazing" difficult for normal individuals to sustain. One patient stared at a swinging cord of a light-switch so intently that, after a time, he came to feel that not the cord but the wall and background were moving back and forth; this led, in turn, to the thought that the world was coming to an end (17, p. 93).

Matussek stresses decontextualization and framing of isolated features for "apperception of delusional significance" (17, p. 94) and generation of delusional beliefs. The very salience or framing of particular items may suggest that something of particular importance or "weighting" is being indicated, conveying an aura of intensified "symbolic content" (17, p. 95). Dis-embedding and a certain derealization can also allow these emerging significances to link up more easily with other, isolated features or meanings floating outside any standard or practical context, and perhaps also separated from normal sorts of reality-claims. "One is much clearer about the relatedness of things, because one can overlook the factuality of things. They don't exist so one has nothing to do with them" (17, p. 96), said one patient, who reported special, revelatory access to meanings ignored by others and stated: "my ability to see connections had been multiplied many times over".

Conrad: apophany and anastrophe

K. Conrad (18) offers a compelling account of global alterations in delusional mood. He refers to the first stage of delusion formation as the *trema* – theatrical jargon referring to stagefright before the play begins. The patient senses that something is in the offing. Most commonly he feels a sense of threat and associated anxiety, depression, inhibition, or indecisiveness (18, pp. 93,105); there may also be anticipatory excitement, exaltation, manic-like euphoria. Despite some difficulties with concentration, there is no clouding of consciousness, but hyper-vigilance, feelings of being hyper-awake (18, pp. 230,249).

What typically ensues in this delusional or pre-delusional mood is the

apophany. "*Apophany*" comes from a Greek word meaning "to become visible or apparent"; it refers to an abnormal, sometimes excruciating sense of meaningfulness – tantalizing but typically unidentifiable – that can affect "internal" (body, stream of consciousness) as well as "external space". The patient attributes these changes to the external world and searches for clues to render the new unpredictable changes more comprehensible.

Often the patient experiences the world as somehow false, inauthentic, or insinuating, and as referring somehow to himself: "I have the feeling that everything turns around me" (18, p. 161). Conrad uses the term *anastrophe* (literally: turning-back or turning-inward) to capture this self-referential, introversive, or self-observing quality – what could be termed a form of "hyper-reflexivity" (15).

Apophany and *anastrophe* are two sides of a coin. Changes in perceived environment (e.g., sense of things being oddly significant, false, or planned) elicit reflection and inhibit spontaneous engaged activity; yet these changes themselves can only occur in the presence of a veritable "spasm of reflexion" (18, pp. 167,199).

Conrad describes progression from subtle to blatant alterations of inner space ("inner *apophany*") that occur during *anastrophe*. The inward focusing actually has an *externalizing* effect, transforming proprioceptive sensations or internal mental threads into something felt as distanced and alien (15,19). An intriguing example is described in a classic article by Tausk and later discussed by Sass as exemplifying hyperreflexivity (15): the patient Natalija's illness began with mild experiences of estrangement from herself and culminated in a full-blown delusion regarding a distant "influencing machine" that determined her every thought, sensation, and movement; it crystallized the *apophany* of her inner space under conditions of "reflexive spasm".

These mutations have been formulated recently as an alteration of minimal or core self or *ipseity* (the basic sense of existing as a unified and vital *subject* of experience), with two complementary facets: hyperreflexivity and diminished self-affection – also associated with disturbance in cognitive/perceptual "grip" or "hold" on the external world (20-22). "Hyperreflexivity" describes how experiences normally tacit emerge into focal awareness, where they are experienced as objects *separate* from self-as-subject, whereas diminished self-affection (also termed diminished self-presence) describes decreased sense of existing *as* an experiencing consciousness or lived body.

Self-disturbance "destabilize[s] the natural ontological attitude and may throw the patient into a new ontological-existential perspective, an often solipsistic framework, no longer ruled by the 'natural' certitudes concerning space, time, causality, and noncontradiction" (11, p. 544), thereby facilitating experiences of the world as staged or mind-dependent, and a grandiose sense of gaining access to deeper layers of reality. Although self-disturbances involve atmospheric and categorically subjective qualities, there is growing evidence that they can be meaningfully measured, thereby bridging phenomenology and scientific demands for reliable measurement (23,24).

Reality-testing and quasi-solipsism

With its sensitivity to *kinds* of reality subjectively felt or ascribed within delusion, phenomenology is cautious about assuming that delusions are "*false* beliefs" about *external* reality. Phenomenologists question the general applicability of the standard "poor-reality-testing" formula assumed in DSM-IV, DSM-5, ICD-10, and much of psychiatry.

Jaspers remarked on "the specific schizophrenic incorrigibility" of (true) delusions, and their peculiar tendency to be associated with irrelevance for action ("inconsequentiality"): "Reality for [the patient] does not always carry the same meaning as that of normal reality… Hence the attitude of the patient to the content of his delusion is peculiarly inconsequent at times… Belief in reality can range through all degrees, from a mere play with possibilities via a double reality – the empirical and the delusional – to unequivocal attitudes in which the delusional content reigns as the sole and absolute reality" (1, pp. 105-106).

But even when delusions reign as "sole and absolute", it is not clear that they are necessarily experienced within the "natural attitude" – the commonsense orientation that takes objects and persons as objectively real and intersubjectively available (2,25). It is noteworthy that patients who claim absolute *confidence* in their delusion, may nevertheless not *act* on its basis. Schreber, for example, often does *not* make claims about the external or interpersonally shared world, claims that could be supported or refuted by evidence independent of the experience itself. His delusional beliefs are frequently described in a way that gives them a coefficient of subjectivity – as when he speaks of appreciating his psychotic experiences "only in part with my mind's eye" or "inner eye" (9, pp. 110,123,136,157,234,235,312). At times he even makes the solipsistic or quasi-divine claim that "seeing" – awareness itself – is "confined to my person and immediate surroundings" (9, p. 322).

If the delusion is believed in the context of something like a (subjectively experienced) natural attitude, one ought to act in relation to that belief. But if the delusion is felt to be true only *for me*, in my mind's eye and for me alone (or, at least, only for me and my *delusional* others), the contradiction is resolved: one need hardly seek evidence for an experience (akin, in some respects, to an imaginary realm) that makes no claim with regard to normal intersubjective reality; one will hardly take action *in actuality* with regard to what one senses as existing in a purely or quasi-virtual realm.

This provides a phenomenological way of accounting for at least *some* instances of the famous "double bookkeeping" of which Bleuler (26) spoke. The very unreality of the delusional

world may, in fact, be the feature that most recommends it, perhaps providing, *in some instances*, the deepest motivation for dwelling in the delusional realm – as Sartre suggests of the "morbid dreamer" who thereby escapes the anxieties and demands of real-world experience (15,27,28).

Summary

The phenomenological approach has focused almost exclusively on delusions in schizophrenia, which (contrary to current usage) are sometimes understood to be the only "true delusions". Phenomenological accounts of delusional mood/atmosphere discuss loosening of perceptual context, promiscuous linkages between de-contextualized elements, a sense of being at the center of things, and alienating hyperreflexivity.

Such a perspective helps to clarify how paranoid, metaphysical, influence-related, bodily, and solipsistic delusions – together with altered experience of self, intersubjectivity, and felt reality – might develop on the basis of overall structural or ontological changes associated with delusional mood and its aftermath. One may wonder whether these constitute heterogeneous features, and to what extent they derive from or reflect some central disruption. The notion of ipseity disturbance (20,22,29) is one hypothesis regarding such a *trouble genérateur* (see 21,23).

NEUROCOGNITIVE APPROACHES

We turn now to a consideration, from a phenomenologist's standpoint, of contemporary neurocognitive theories of delusion. We focus on prominent recent representatives of two domains: a) the phenomenological hypotheses of minimal-self or ipseity disturbance (20) and hyperreflexivity/alienation (15), introduced above; b) neurocognitive models (30) postulating aberrant salience (31) and prediction error offered by Fletcher and Frith (32) and especially Corlett et al (33), with later consideration of efforts to relate the concept of the default mode to schizophrenia and delusions (34-36).

We consider three, somewhat overlapping, issues: a) the consistency – within certain limits – between phenomenological perspectives and the prediction error and salience dysregulation models; b) the problematic tendency of contemporary neurocognitive (as well as cognitive-behavioral) accounts to adopt an overly homogenizing and insufficiently "ontological" perspective on "delusion"; c) some ways phenomenology might broaden the contemporary neurocognitive vision, expanding the range of testable hypotheses. Given phenomenology's focus on delusions in schizophrenia, we mostly deal with that particular syndrome or disorder.

Compatibility of phenomenology with prediction error and salience dysregulation accounts

The prediction error model assumes that principles of Bayesian inference (method whereby probability estimates are continuously updated as additional evidence is acquired) play a crucial role in human perception and learning. Applied to delusion, the model introduces three postulates.

The first is that the patient experiences an exaggerated sense of strangeness, novelty or surprise – due to "disrupted prediction-error signaling" (37, pp. 2387,2388) – of the significance of what, objectively speaking, are minor discrepancies between perceptual expectancies and perceptual input, thereby "engender[ing] prediction error where there ought to be none" (33, p. 357) ("noise in predictive learning mechanisms").

The second is that this disconcerting sense of anomaly, whereby objectively "redundant or irrelevant environmental cues" (33, p. 347) nevertheless seem "strange and sinister", readily gives rise to delusions that serve to account for the sense of anomaly.

The third is that this over-emphasis or over-"weighting" (32) also skews future perceptual and cognitive expectancies ("empirical prior beliefs" (33, p. 347)) in unrealistic, dysfunctional, often delusional directions, because of the distorting influence of input that should have been filtered out as irrelevant or inconsequential (as mere noise) and the attempt to understand the anomalous experience. Because "the errors are false" (32, p. 55), no amount of associated updating of beliefs can ever adequately model the world; hence "prediction errors will be propagated even further up the system to ever-higher levels of abstraction". Dysfunctions in the mesocorticolimbic dopamine system, right prefrontal cortex, and glutamate transmission may underlie these dynamic processes.

Corlett et al's (33) prediction error formulation offers a rich and stimulating neurobiological account. They aim to provide a comprehensive and unifying framework, postulating "a singular dysfunction" (33, p. 361), or "single factor, prediction error dysfunction for delusion formation and maintenance", underlying *all* delusions, across diagnostic groups – a view consistent with a "complaint-oriented approach" (38, p. 221) and the U.S. National Institute of Mental Health's initiatives to focus on symptoms or "problem behaviors" (39, p. 635) and "aberrant systems that implement psychopathology" (39, p. 633) rather than syndromes (40). Our own preference is for transcending this potentially misleading polarity between symptoms and syndromes, by emphasizing how "syndromes" (such as schizophrenia) can embody distinctive global modes of psychological life that may render symptoms (such as delusion) more heterogeneous than they otherwise appear.

The compatibility of phenomenological and prediction error (and related) accounts has been discussed in two recent articles on salience dysregulation and source monitoring as possible neurocognitive correlates of the disturbance of minimal-self/ipseity emphasized by phenomenologists (41,42; see also 43 for an alternative discussion of phenomenology/neurobiology/delusion). Though Corlett et al's (33) model particularly emphasizes "prediction error",

it incorporates both the aberrant salience theory of Kapur (31) and Frith's model of source monitoring (44-46).

Already in 1992, Sass (15) discussed neurocognitive accounts consistent with his emphasis on the "hyperreflexive" and alienated aspects of schizophrenic subjectivity; he linked the latter directly to phenomenological accounts of delusion formation by Conrad and Matussek, and to both Hemsley and Gray's model of disturbed expectancies ("weakening of the influence of regularities" that normally orient and constrain ongoing perceptual processes) (47, p. 18; 15, p. 69); and Frith's (45) diminished efferent "feedback from willed intentions" (neurocognitive feedback indicating to oneself that one's own bodily movement is an intentional action) (15, p. 435) undermining normal self-experiences of possession and control.

Important details of the neurocognitive model have obviously changed over two decades. The psychological processes now postulated are not very different, however, since the key element of both Hemsley's expectancy hypothesis (prominently cited by Corlett et al, 33) and the current prediction error model is "mismatch between expectation and experience" (33, p. 345) and the consequent prominence of (inappropriate) salience and surprise. Corlett et al (48) present their Bayesian prediction error model as an extension, in terms of "underlying neurochemistry", of the perspectives offered by Hemsley and Kapur. Sass (15,49) notes that this disruption of expectancies would affect experience not only of the external world (Hemsley's original emphasis; Conrad's *external* apophany), but also of core-self and lived body (Conrad's *internal* apophany). Although these self-aspects are not stressed in Kapur's (31) account of salience dysregulation, the issue of agency is extensively discussed in prediction-error theory, with prediction errors in self-generated action explaining both delusions of motor control and excessive sense of agency (33).

It is noteworthy, however, that phenomenologists have emphasized (e.g., 15) the potential contribution of disturbed self-experience – especially of lived-body or body-schema (implicitly sensed body-awareness that serves as *background* to our experience of the world) – to *constituting* the *overall* ontological transformations, including those pertaining to the external world, inherent in delusional mood or delusion formation. These ontological transformations, expressed and grounded in distortions of the lived-body (as locus of basic selfhood), are, in any case, necessary considerations for accounting for the "bizarreness" (50) of many *schizophrenic* delusions and experience more generally, which seem less a matter of straightforward threats from the mundane environment than more foundational alterations of experience of self, lived-body, or world. Indeed, many schizophrenic delusions are closely interwoven with altered bodily ways of being, which they in a sense express (51).

Consider Natalija's classic influencing-machine delusion and Schreber's solipsistic delusional world of "nerves" and "rays". Each manifests, in a particularly blatant way, the experience of being alienated from one's own corporeal and mental feelings and movements (while also taking these feelings and movements – even one's own subjectivity – as prime objects of attention), together with concomitant derealization of the external world (15,28).

Such delusions might be better captured by perspectives that favor "enactive" or "radical embodied" approaches to cognition (52,53), inspired by phenomenology's – especially Merleau-Ponty's (54) – stress on how world-experience is imbued with the perceiver's own implicit sense of bodily capacities and dispositions. Here there is at least the *appearance* of conflict with the more intellectualistic-sounding prediction-error formulations, e.g., regarding "false *inference*" (33, p. 346, emphasis added) and "maladaptive *beliefs* that *misrepresent* the world", with "belief" defined (within the Bayesian framework) as "the subjective probability that some *proposition* about the world is true" (32, p. 50, emphasis added). The "beliefs" and "propositions" at issue pertain to spontaneous bodily action/perception, yet are described on the model of intellectual conjecture or formulation, reminiscent of the explicit "conjectures and refutations" of scientific theorizing (55; see also 56 and Merleau-Ponty's critique of intellectualism (54)); they seem to pertain to facts *within* the world rather than to alterations in global foundations or self-world structures. Closer to the spirit of phenomenology (or, at least, its vocabulary) is an attempt to link disturbances of predictive precision with diminished "*self-presence*" (ipseity) and, in turn, with associated delusions (57).

We see, then, that there is substantial compatibility between contemporary neurocognitive and phenomenological accounts. Phenomenology, however, with its commitment to subjective dimensions, stresses the *constitutive* role of basic self-experience and ontological aspects of delusional mood as crucial to characterizing delusions.

The paranoia paradigm

Our second point criticizes the tendency to view "delusion" (using this term in the broad, contemporary sense) as a distinct, even modular phenomenon, and to assume the possibility of a unifying account that cuts across diagnostic entities and phases of illness, offering "a unifying explanation for delusions with disparate contents" (33, p. 346) by postulating "a singular dysfunction" (33, p. 361) or "single factor".

We acknowledge the remarkable theoretical ingenuity and subtlety especially of Corlett et al's (33) hypotheses, based on an overarching prediction error model that views mind/brain as an inference machine. To us, however, the Bayesian prediction error model lacks face validity as an account of (at least) such delusions as those involving profound guilt, death, or bodily disintegration, or wealth and power, that are common in severe depression and mania, or of solipsistic grandeur and metaphysical revelation found in some chronic/

withdrawn patients with schizophrenia (e.g., 58,59). Such delusions seem likely to be more decisively linked to different psychological states, not the "powerful and uncomfortable experience" (33, p. 353) of uncertainty and surprise, but rather self-hatred, despair, devitalization, elation, or the possibilities for grandiosity or awe inherent in solipsistic withdrawal. The emphasis on surprise, novelty, or strangeness may apply best to paranoid delusions, representing what we term the "paranoia paradigm": the tendency to view literal beliefs about external threat or attack as constituting the prototypical instance of delusion.

Paranoid/persecutory delusions frequently occur in schizophrenia and delusional disorders (60-62), which, historically speaking, are the delusional conditions *par excellence*; they are common in affective psychoses and certain neurological conditions (63). This is one reason why such delusions may play a disproportionate role in inspiring neurobiological and cognitive theories. Another reason concerns the understandability and at least rational possibility (non-bizarre quality) of many paranoid delusions (especially outside schizophrenia): this means that they more readily conform with both commonsense and standard psychiatric assumptions about the nature of beliefs. This understandability, however, may align this kind of delusion with what Jaspers termed a "delusional idea" – something that can be "comprehend[ed] vividly enough as an exaggeration or diminution of known phenomena" (1, p. 577) (namely, anxious scanning and sense of threat).

Some would stress that psychotic delusions are not, in fact, categorically different from what Jaspers termed "delusion-like" ideas, overvalued ideas, and normal beliefs (64). Such a view has been influential in cognitive models of delusions (65), cognitive-behavior therapy (CBT) for delusions (66), psychometric measurement of delusions (67), and neurocognitive attempts to model delusions as "maladaptive beliefs that misrepresent the world" (33, p. 346). The operative assumption is that all such phenomena lie on a continuum, and that all involve claims about the world that are believed by the patient more or less from within the (subjectively experienced) "natural attitude". There is merit in questioning absolute and categorical claims. But, as indicated, consideration of lived dimensions of key delusional experiences suggests the importance of appreciating certain qualitative differences regarding implicit reality-claims or experiences of reality.

Some delusions, especially persecutory, may well involve "mistaken beliefs" that prompt action. But, as Jaspers' observations suggest, not *all* delusions are of this nature. Many schizophrenia patients, especially perhaps withdrawn individuals, describe forms of double bookkeeping or quasi-solipsistic subjectivization (27,28). Patients with grandiose and guilt-based delusions are less likely to act on delusions, despite being more certain and more impervious to counter-evidence (68,69; see also 70,71). Such delusions may pertain to what the patient experiences (albeit ambiguously) as occurring only in another realm where the usual sources of refutation – or motivations for action – are rendered phenomenologically and logically irrelevant, or at least dubious. This begs for a distinction between empirical or ontic delusions and those of a more autistic, solipsistic, or ontological nature (4,15,28,72). Both should, however, be recognized as ideal types, involving transitional and overlapping possibilities rather than dichotomous forms. Cognitive scientists tend to base their models of delusion formation on formal logic and notions about scientific discovery (e.g., 73). But once the limitations of the belief model or "paranoia paradigm" are recognized, the notions of aesthetic or imaginative experience may seem equally or more relevant (27,58).

Thus, at least *some* delusions, especially in schizophrenia, are not straightforward instances of mistaken *belief*, in the usual sense of the term, or of "false inference" (33, p. 346) that "misrepresent" objective reality. To recognize this should force us to raise questions regarding underlying pathology (e.g., the role of hypothesized "deficits" or biases in cognitive processes, including supposed "reasoning abnormalities", "top-down reasoning impairments" or lesions in "belief evaluation" regions of the brain), and also regarding potential psychological treatments: for instance, can proffering counter-evidence really be the true therapeutic element in successful CBT for psychosis (74)?

Expanding the range of neurocognitive hypotheses

The tendency to conceive of delusions in terms of hypersalience and surprise, typically involving a sense of ontic threat from external reality, may be related to a certain asymmetry *within* the prediction error account.

Both Fletcher and Frith (32) and Corlett et al (33) do acknowledge that prediction error can be awry through overweighting but also through *under*-weighting or *under*-emphasizing of prediction error or perceptual anomaly. Thus, Fletcher and Frith (32) speak of "relatively augmented response to stimuli that should be neutral" (32, p. 53), but also of "relatively suppressed response to stimuli that [since *un*expected] should be relevant and important", noting evidence for *both* in schizophrenia (see also 37). Despite this recognition, their accounts of delusion formation clearly emphasize *exaggerated* prediction-error signaling: how "excessive bottom-up signaling" (48, p. 517) or "aberrant novelty… signals drive attention" (33, p. 347) or "grab attention" (32, p. 55), demanding "an explanation or an updating of belief… [which in turn] forms the germ of a delusional belief".

A striking feature of schizophrenia's characteristically paradoxical nature is that schizophrenic persons seem unusually capable *not only* of finding the banal to be strange (which would accord with hypersalience), *but also* of finding the strange banal (*hypo*salience).

Sass (15) cites the neglected work of Polyakov (75) on disturbances of "probability prognosis". Using tachistoscopic studies, Polyakov demonstrated exaggerated openness in schizophrenia:

enhanced ability to quickly identify, accept, and take in stride phenomena that most people would find anomalous, strange to the point of being difficult to recognize. Related tendencies are mentioned by Fletcher and Frith and by Corlett et al, who speak, respectively, of dream-states in which experiences "are often bizarre yet accepted without question" (32, p. 52) and of enhanced capacity, in schizophrenia, to recognize a concave mask rather than "correcting" to the standard convexity of a face (33, p. 352). They do not, however, clearly relate this propensity (for taking anomalies in stride) to delusions.

We suggest that this latter propensity may often foster an attitude – call it an "anything-goes" orientation – that is intimately related to the characteristically schizophrenic loss of commonsense or natural self-evidence (76,77), and thereby to delusion formation as well. An "anything-goes" orientation obviously undermines the overall grounding in habitual, commonsense reality that ordinarily bolsters our ability to recognize and reject that which is eminently implausible; hence this orientation may facilitate the genesis, acceptance, and persistence of objectively implausible meanings and connections that can be central in delusion formation, especially in some "bizarre" and solipsistic delusions characteristic of schizophrenia. The lack of constraints may foster a kind of "pathological freedom" (15, p. 127) that is characteristic of schizophrenia. Recall Matussek's patient: "One is much clearer about the relatedness of things, because one can overlook the factuality of things" (17, p. 96). In this sense it could underlie *some* – though not all – instances of the so-called "jumping-to-conclusions" style studied by CBT theorists.

This mode of experience – "bizarre-as-banal" – may be associated with underweighting rather than overweighting of the significance of prediction errors, involving distinct patterns of activity in neural pathways and in neurotransmitters such as dopamine and glutamate. Psychologically, it may be associated with passive withdrawal and hyperawareness, perhaps characterized less by overemphasis on than by relative *indifference* to anomaly. Ipseity or minimal-self-experience seems likely to be altered in this default, anything-goes mode, probably in the direction of disengagement and diminished presence or vitality. Further, this orientation may have some relationship with what has been termed the "default-mode network" (DMN) activity, already found to be related to the generation of positive symptoms, hallucinations, and possibly delusions as well (36,78-80).

The DMN – first identified by Raichle (81) in 2001 – is activated when there is withdrawal from practical, world-oriented activity in favor of self-referential processing, autobiographical recall and mind-wandering (82,83). The network includes medial prefrontal cortex, posterior cingulate/retrosplenial cortex, and left and right inferior parietal lobules (36). Various experts have mentioned a "give and take" between DMN and "task-positive" systems ("reciprocal patterns of activation and deactivation") (82, p. 1276), since DMN normally suppresses the attention and salience systems or central-executive network systems (which involve dorsolateral prefrontal cortex and parietal regions) activated in situations requiring response selection and working memory that presumably increase weighting of anomalous perceptions (84).

Interestingly, in schizophrenia, there seems to be poor deactivation of the DMN even when such persons are attending to external stimuli (36,84,85), suggesting "reduced engagement with the external world" (82, p. 1276). This finding suggests that a dreamlike, introversive, or subjectivistic orientation can prevail even during ostensible engagement in practical action.

The importance of this sort of introverted orientation is discussed by Sass (15) in relation to the "hypofrontality" (deactivation of dorsolateral prefrontal cortex) often found in schizophrenia. Sass argued that this hypofrontality should be understood *not* as decline of higher or more abstract functions (a standard view at the time), *but rather* as withdrawal from "goal-directed action" (15, p. 389), "orientation to the external world", or pragmatic cognition in preference for "more introverted and detached modes of cognition" (15, p. 556) – modes that could underlie characteristic "transformations of self and world" (15, p. 390) that occur in schizophrenia, including perceptual disorganization, abnormal salience, and introversion conducive to delusions and hallucinations.

Gerrans (34) has offered an original but compatible discussion of the default mode's role in generating delusions. Whereas he emphasizes suppression of "reality-testing", we speak of an alternate ontological modality in which intersubjective reality is suspended.

Thus, there may be at least *two* abnormal modalities ("overweighting" and "underweighting" of prediction errors), apparently opposed, *both* common in schizophrenia and *both* related to development of delusions – albeit not necessarily delusions of the same type. But what of the relationship *between* these two modes?

A possibility consistent with Kapur (31), Fletcher and Frith (32), and Corlett et al (33) is that the overweighting would have pathogenetic priority, coming first, and *then* giving rise to an underweighting that results from fatigue or withdrawal. Neurobiologically, hyperactivation of salience network would be followed by hyperactivation of DMN and concomitant suppression of salience and attention systems. Psychologically, anxious hyperawareness of anomaly would be followed by psychological withdrawal or non-reactivity, perhaps because constant strangeness accustoms one to the strangeness of the strange. But in *some* schizophrenic patients – perhaps those of a more "disorganized" type and with insidious onset – the "anything-goes" orientation might be more crucial to the initial formation of delusions. Delusions are less prominent in such patients, but they certainly occur, and clearly demand explanation in any comprehensive account.

Another possibility, however, is that a kind of "anything-goes" orientation

could have a more *intrinsic* relationship to the banal-as-bizarre experience. Many patients might clearly recognize or perhaps sense – at some level of implicit but encompassing (ontological) awareness – that a world in which things loom up as salient for no apparent reason (banal-as-strange, due to "overweighting") is, in fact, a distinctly *different* world involving different "feelings of being" (86,87) and in which standard assumptions or reality-criteria are suspended. The very fact of these changes would undermine the "natural attitude", leading to feelings that the world is somehow unreal and therefore no longer subject to standard constraints of logic and realism.

Perhaps, then, even *without* an underweighting of Bayesian prediction errors, there could be a shift to an "anything-goes" attitude, albeit one that may also *differ* from the more purely permissive, less anxiety-ridden "anything-goes" of the prototypical disorganized schizophrenia patient. This would accord with some findings indicating reduced functional network connectivity in schizophrenia, especially reduced mutual suppression between salience and default-mode networks (84), such that "systems normally inhibited by the DMN (e.g. the salience system) may slip from its control" (82, p. 1276), allowing DMN and salience system to be activated simultaneously.

Obviously we are in the realm of speculation. These hypotheses derive, in large measure, from patient self-reports and theoretical conjectures grounded in phenomenological philosophy and psychopathology. They are, however, also grounded in the neurobiological findings and hypotheses of contemporary neuroscience.

Summary

The phenomenological perspective is congruent with (and has anticipated) many aspects of contemporary neuroscientific approaches to delusions, including models emphasizing salience dysregulation, prediction error, and hyperactivation of DMN.

A phenomenological approach supports the relevance, for many delusions, of the now-prominent overweighting-of-prediction-error model, while also suggesting other aspects of, and pathways to, delusion that are not addressed by this model. These latter include forms of distorted ipseity or minimal-self and also alterations of ontological dimensions neglected outside phenomenology – such as overall derealization, solipsism, and an "anything-goes" orientation.

In our opinion, the diversity of these factors raises doubts about the wisdom of viewing delusion as a unitary phenomenon – whether in experiential, psychological, or neurobiological terms.

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Delusions, epistemology and phenophobia

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Sass and Byrom (1) reconsider the phenomenology of delusion and its fit with contemporary accounts from cognitive neuroscience. Starting from their considerations, I will highlight some basic problems of the epistemology of the DSM-III+ (i.e., all versions of DSM from DSM-III to DSM-5).

For psychiatrists solely trained in DSM-III+ based psychopathology, Sass and Byrom's article may seem as a reminiscence of non-empirical speculation of a pre-scientific era, expressed in a "poetic language" that was finally abandoned in the construction of operational vocabulary in DSM-III. This operationalization of the diagnostic terms was anticipated to produce a rapid etiological progress due to the unambiguous phenotypic descriptions. However, these hopes have not materialized despite massive research efforts with an accumulation of a bewildering diversity of empirical findings.

This "etiological failure" is usually ascribed to an unexpected complexity of the brain (2) or to an assumed heterogeneity of the DSM-III+ diagnostic phenotypes, unfit for causal exploration (3). However, the etiological failure may also have been due to a misguided epistemology of the DSM-III+ (4). Indeed, the case of delusion presented here (1) points not so much to a still insufficient resolution power of biotechnology but rather to a more basic descriptive problem of DSM-III+, that is, an overly simplistic psychopathology, with potentially distorted phenomenological distinctions (4).

In DSM-III and IV, delusions were defined as "false beliefs due to incorrect inference about external reality". The DSM-5 definition is more laconic: "fixed beliefs that are not amenable to change in light of conflicting evidence". These definitions are *by no means* "operational" in any scientific sense of the term and are in many respects also empirically incorrect (1,5). Most importantly, they all deal with what have been consistently considered as "delusion-like ideas", "secondary" or "second-rank" delusions, which reflect variously determined judgmental errors. However, it is the "true", "primary" or "ontological" delusion (1) that constitutes the central concern of psychopathology, because it holds a key to grasping the mental life in schizophrenia, with pathogenetic and diagnostic implications (5).

Primary delusions exhibit an intrinsic affinity to auditory verbal hallucinations and to passivity phenomena (6,7). The DSM-III+ attempted to compensate for omitting the primary delusions by introducing a novel category, i.e., "bizarre delusion". This was a delusion, defined as a *false belief due to incorrect inference*, further possessing a propositional *content* deemed to be "bizarre", i.e. (in DSM-5) "clearly implausible, not understandable to same-culture peers and not derived from ordinary life experiences". The successive changes in the definition's exact wording from DSM-III to DSM-5 were solely motivated by reliability concerns, whereas it was not considered that the content of a delusion, taken in itself, i.e., outside of its *psychopathological context*, has a limited diagnostic value (5).

Rather, the validity of "bizarre delusion" was justified by brief references to Kraepelin's remark that delusions in schizophrenia are often "nonsensical" and to Jaspers' notion of "un-understandability" (5). "Bizarre delusions" were exemplified by the passivity phenomena. Yet, the delusions of influence (e.g., delusion of thought insertion, accounting for experiencing of thoughts deprived of their usual sense of mineness/ipseity) are explanatory-cognitive efforts and hence belong to the category of delusion-like ideas, secondary – or second-rank delusions (5). Unfortunately, the main body of neurocognitive research into delusion, psychosis, "insight", as well research of psychotherapeutic approaches to delusions (8), have been committed to this latter, i.e., secondary notion of delusion (as a cognitive mistake), which has basically nothing to do with the "primary", "ontological" or "true" delusions of schizophrenia (1).

From a phenomenological perspective, primary delusions are *not* originally cognitive errors but are essentially *experiential* phenomena with affective or *pathic* roots – an aspect well illustrated by Conrad's accounts of *trema* and "intensified ground-affectivity" (1). In this sense we may talk of delusional *experience* or, perhaps even more appropriately, of *a psychotic core experience*, shared by delusions and auditory verbal hallucinations. This is best described as an *affection* (structurally not unlike a sensation, e.g., a tooth-ache), which articulates itself in the midst of the patient's innermost subjective, private sphere (6,7,9). It is, writes H. Ey, a "modification within the self" with an emergent sentiment of alienation, otherness or alterity (*l'éxperience d'alterité*) (6, p. 417).

The primary delusion arises as a *revelation,* i.e., an affective, non-conceptual articulation of meaning that only subsequently becomes cognitively elaborated and dressed with propositional delusional content. Noncompliance with treatment and incorrigibility of such delusions stem from their roots in the original first-personal (egological) affection (no one ever doubts his own tooth-ache; in fact, it would be absurd to do so) (9).

Primary delusions are not self-contained, *atomic symptoms* but reflect more basic alterations of the structure of consciousness, variously named (e.g., autism, ipseity-hyperreflexivity disorder, lack of "natural evidence", "altered awareness of reality", etc. (10)), with an emergence of another ontological

framework, no longer ruled by the axioms of everyday "natural attitude" (9).

It is not possible to advance clinical and scientific psychiatry without intimate familiarity with psychopathological phenomena and without a *general conception* (framework) of the nature of subjectivity; in Jaspers' words, "a knowledge of what people experience, and how they experience it". Unfortunately, current diagnostic manuals offer no more than a behaviouristically biased aggregate of mutually independent, lay-language descriptions that fail to faithfully reflect pathological alterations in the mental realm. Such *phenophobia*, if not remedied, will in all likelihood weaken credibility of clinical psychiatry and continue to undermine research efforts.

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Phenomenological models of delusions: concerns regarding the neglect of the role of emotional pain and intersubjectivity

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Sass and Byrom's paper (1) describes one phenomenological and several neurocognitive models of delusions and then proposes a synthesis. The authors put forward a model in which alterations in self-experience interact with neurocognitive processes such that persons over-value information that should be ignored and withdraw "from practical, world-oriented activity in favor of self-referential processing", ultimately arriving at convictions which may be profound barriers to wellness.

We support the integration of neuroscience and phenomenological models. These different approaches are rarely considered as complementary even though any comprehensive model of severe mental illness requires that both the subjective phenomena and neurocognitive processes involved be accounted for and reconciled. We also agree with the authors' reflections that no single psychological, neurobiological or phenomenological model is likely to explain delusions. In this commentary, however, we will suggest that the authors' synthesis neglects substantial bodies of knowledge about delusions, including their instability within the flow of daily life, temporal links between painful affects and the presence of delusions, and correlates with difficulties forming ideas about the thoughts and experiences of others. In what follows we will detail each of these points and suggest that ignoring this literature risks dehumanizing the dilemmas at the heart of delusional experience, something which could have deeply negative consequences for treatment.

To begin, we agree that understanding delusions primarily as miscalculations based on neurocognitive abnormalities does not match the evidence. We, however, see that the core problem with purely cognitivist explanations is that delusional beliefs are unstable and often emerge in particular intersubjective contexts. People with schizophrenia may be delusional during some but not other periods of the day, and may be delusional about certain issues but not others (2,3). The instability of delusions poses a problem for the cognitivist models, as well as for the phenomenological model offered in Sass and Byrom's paper. Why would delusional processes fluctuate so dramatically if they are a matter of the trait-like deficits proposed?

A related problem is that multiple studies suggest that fluctuations in delusions often follow alterations in emotional state. Threats to self-esteem and the emergence of clearly discernable forms of emotional pain have been found to predict the occurrence of positive symptoms in multiple studies (4,5). This would seem to suggest that delusions are not merely miscalculations

based on neurocognitive deficits or the product of fundamental alterations in the sense of self, as the authors describe. Instead, if pain triggers delusional experience, it may be that delusions are in part attempts, albeit ineffective ones, by human beings to explain or communicate their pain to other human beings. This is also consistent with work from evolutionary psychiatry suggesting that paranoia may be a dysfunction of the basic threat detection system.

It has been suggested that persecutory delusions may emerge when persons do not feel that they belong within any group and so, in the absence of a sense of safeness and security, they feel constantly threatened and ultimately explain that in terms of imagined threats (6). Importantly though, delusions may at different times stem from very different motives. While delusions may express distress at some moments, at other times they may function as a means to ward off emotional connections with others. In other words, their oddness may be intentional and serve the purpose of remaining unknowable to prevent the emergence of pain (7).

Another literature that is not considered here concerns the difficulties many with psychosis have forming complex integrated ideas about the subjective experiences of other persons, sometimes referred to as theory of mind and metacognition (8,9). This would seem relevant in two senses. Persons unable to notice specific things about others or to appreciate the perspectives of other people might well adopt delusional stances as a fail-safe response to uncertainty. They would also seem less likely to be able to adjust their views based on what others think, as others' views would be inaccessible.

Sass and Byrom do discuss a general withdrawal to a solipsistic state, but we suggest looking at something different: problems that occur when persons with psychosis fully try to focus or interact with others, something that seems essential for any coherent model of how delusions unfold as they do in the flow of daily life. Of note, alternative models not mentioned by Sass and Byrom do exist for understanding delusions and their place in the human condition. These include the work of Salvatore et al (10), who suggest that the experience of ontic threat interacts with real life experiences, cognitive biases and deficits in the ability to understand others to produce at least certain kinds of delusions.

In summary, Sass and Byrom's view seems to neglect well-established links of delusions with emotional pain and metacognition, and this carries several hazards. In our opinion, the risk is to cast delusions as exotic phenomena and therefore, mistakenly, as mental states which are incomprehensible rather than understandable forms of human experience. This may further result in positioning persons with delusions as beings removed from pain and the most central elements of human experience.

At the level of clinical practice, we see an even more significant danger. Sass and Byrom's model seems to us to risk relieving clinicians from the charge of understanding the humanity of their patients and could well result in clinicians standing at a distance from their patients and their suffering.

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The interpersonal world of psychosis

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Sass and Byrom (1) do a fine job in explaining the phenomenological approach to delusions, linking themes in phenomenological psychopathology to work on predictive coding, and emphasizing the heterogeneity of delusional experience. Delusions, they maintain, presuppose more enveloping changes in a person's sense of self, body, and world. In this commentary, I will address a theme that is not so prominent in their discussion of these changes but implicit throughout: the interpersonal aspect. In so doing, I seek to complement and elaborate upon their account, as well as point to some avenues for further enquiry.

In *General Psychopathology*, Jaspers offers the following brief remarks about belief-formation and the social world: "Normal convictions are formed in a context of social living and common knowledge… The source for incorrigibility therefore is not to be found in any single phenomenon by itself but in the human situation as a whole, which nobody would surrender lightly. If socially accepted reality totters, people become adrift" (2, p. 104). We can distinguish two complementary themes here. First of all, our belief-formation processes depend upon our relations with other people. For example, I have argued elsewhere that a kind of non-localized *trust* has a central role to play. For our epistemic practices to be guided by others, those others must be regarded as epistemically competent and also well-meaning. This is not something we ordinarily accept in the form of a debatable proposition. Rather, our default way of experiencing and relating to other people involves, amongst other things, a kind of habitual trust (3). Second, the beliefs that we do form are embedded in a consensus world, in a taken-for-granted background of shared knowledge and practice. Hence belief-formation and belief-content are both shaped by a certain "style" or "form" of interpersonal experience and relatedness.

However, this point is not specific to belief. How our surroundings *appear* to us similarly implicates our relations with specific individuals and with people in general. The phenomenologist and psychiatrist J.H. van den Berg notes how a situation can *look* quite different, depending on *who* we are with. We avoid certain people because we want to keep our surroundings "undamaged", while the company of others is pleasant in that "the objects encountered come to no harm" (4, p. 65). In fact, human experience is interpersonally regulated to such an extent that profound and prolonged social deprivation can erode the capacity to distinguish one's body from one's surroundings, imagining from perceiving, and wakefulness from dreaming (5). Pronounced alterations in the overall *form* of interpersonal experience, in how one encounters and relates to people in general, are thus inextricable from wider-ranging changes in the structure of experience and thought. The point can also be applied to predictive coding models: in addition to exploring how isolated organisms make predictions, detect errors, and compensate for those errors, we ought to consider the roles played by intersubjective regulatory processes.

As Sass and Byrom observe, psychosis involves estrangement from the "commonsense" world. Once we emphasize that this world is essentially a public, consensus world, it becomes clearer why there is a change not just in the content of one's beliefs but also in the *way in which one believes*. Believing that *p* is the case and that *q* is not the case involves regarding *p* but not *q* as integral to the public world. However, if none of a person's beliefs are rooted in a public world, she cannot make sense of the contrast between *p* and *q* in that way. So, when she asserts that something "is the case" or "is not the case", a different *kind* of conviction must be involved.

Global social estrangement could take various different forms. For instance, R.D. Laing famously describes a predicament where others appear *only* in the guise of existential threat, thus cutting one off from kinds of interpersonal relation that are more usually implicated in the formation, sustenance, and revision of belief (6). But other changes in the structure of intersubjectivity that have the effect of cutting one off from other people in general would similarly impact upon the form of experience and belief. Interpersonal experience in psychosis is therefore potentially quite variable.

As well as being inseparable from the structure of delusional experience, interpersonal processes plausibly have an important *developmental* role to play. It is increasingly acknowledged that there are significant links between trauma and psychosis. In particular, childhood trauma and abuse are claimed to increase vulnerability to psychosis, with some authors maintaining that up to 85% of adults with schizophrenia diagnoses have suffered childhood abuse (7,8). It is plausible to suggest that early attachment patterns, which nurture a kind of *affective trust* in others, have an important influence on how one later comes to experience and relate to the interpersonal world as a whole. These patterns can be derailed – to varying degrees – by childhood trauma. Associated epistemic biases in adulthood include an intolerance of ambiguity, inflexible and dogmatic thinking, and a tendency to make judgements based on insufficient information (something that may arise – in part – from a failure to treat others as reliable sources of information) (9).

Amongst other things, diminished affective trust would interfere with what Csibra and Gergely call "natural pedagogy", a process whereby ostensive cues from others foster credulity so as to facilitate the transmission of general information about the social world (10). Thus, without a certain *way* of relating to others, the sense of being rooted in a public world would be compromised from the outset, leading to epistemic dispositions and a more general *way of finding oneself in the interpersonal world* that could render one susceptible to further unpleasant social experiences and, ultimately, to psychosis. Of course, there may also be very different cases where an endogenous "delusional atmosphere" arises independently of interpersonal relations, with salience dysregulation then driving disruptions of intersubjectivity (7). But, even in this kind of scenario, how others respond could play various roles in determining outcome.

Hence, a profound and pervasive estrangement from other people is central to many, perhaps all, variants of delusional experience. It sets one adrift from relations that regulate the form, as well as the content, of experience and belief. Furthermore, altered interpersonal experience is not merely integral to the kinds of experience that

Sass and Byrom describe; it has important developmental roles to play too.

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The intersubjectivity of delusions

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Sass and Byrom (1) convincingly argue for the need to systematically investigate the lived or subjective experience of schizophrenic delusions. Moreover, they connect phenomenological accounts of delusion formation with current neurocognitive models of salience dysregulation and prediction error. I fully subscribe to this approach, yet I want to draw the reader's attention to an additional dimension of delusions which may be elucidated by a phenomenological and enactive approach.

To begin with, traditional notions such as incomprehensibility (Jaspers), decontextualization (Matussek) or *apophany* (Conrad), but also more recent concepts presented by Sass and Byrom such as ipseity disorder, hyperreflexivity or schizophrenic solipsism, may convey the impression that schizophrenic delusion is a rather individual or subjective phenomenon, implying a withdrawal from sociality into a dream-like inner world. Similarly, the neurocognitive models of prediction error signalling or of hypersalience attempt to explain delusions by reference to basal cognitive dysfunctions that lend abnormal significance or strangeness to normally irrelevant "environmental cues". What threatens to be overlooked in both cases is that schizophrenic delusions are essentially *intersubjective phenomena*, both in form and content.

First, Sass and Byrom rightly question the standard account of delusions as "mistaken beliefs" about objective facts in the world. Bizarre delusions aside, in most cases the psychiatrist will hardly be able to *empirically falsify* the patient's delusional claims – but this won't even be necessary. Delusions typically manifest themselves in an *intersubjective* situation, namely as a peculiar inability or refusal of the patient to adequately take the other's perspective into account, to understand his doubts, to try to make himself adequately understood, etc.. In other words, delusions appear primarily as a specific *disturbance or breakdown of communication*: the mutual comparison and alignment of perspectives fails.

Nevertheless, regarding content, schizophrenic delusions notoriously show *a pervasive reference to others* by whom the patient feels observed, spied at, persecuted or manipulated. Even though the others often remain hidden, act covertly or in a roundabout way, the patient nevertheless has the impression of being in the centre of their gazes, intentions and actions. Conrad's *trema* or "stage fright" in beginning psychosis as well as his notion of *anastrophe* ("everything turns around me") point to the *self-centrality* of the schizophrenic person, experienced as if being on a clandestine stage, in the midst of a mysterious play that he tries in vain to decipher (P. Weir's *Truman Show* is a movie which patients often mention in order to describe their experience). Similarly, the hypersalience of environmental cues in most cases refers to *social* situations and significances (meaningful gazes, "telling" gestures, strange people walking by, etc.), resulting in an experienced threat from evil intentions of others rather than from the natural world.

Thus it seems that an adequate analysis of the phenomenon of delusion has to take its intersubjective dimension into account (2). Our experience of the world is not a solitary achievement, but is based on a continuous intersubjective co-creation of meaning. We live in a shared life-world because we continuously create and "enact" it through our coordinated activities and "participatory sense-making" (3). This implies circular processes of mutual understanding, negotiation of intentions, alignment of perspectives and reciprocal correction of perceptions – processes that take place in every interaction and communication with others.

An essential presupposition for these processes is the capacity of *shared intentionality* or *perspective taking* – that means, to transcend one's primary, egocentric perspective and to grasp others' intentions and point of view. This suspends the primary self-centrality

that is ultimately rooted in the subjective or lived body. Intersubjectivity in its full sense is thus based on the ability to oscillate between an ego-centric, embodied perspective on the one hand, and an allo-centric or decentred perspective on the other, without thereby losing one's bodily centre of self-awareness. This decisive step of human cognitive development may also be summarized as reaching the *excentric position*, a term coined by German philosopher H. Plessner (4) to denote a third or higher-level stance from which the *integration* of the ego- and allo-centric point of view is possible.

Thus, intersubjectivity implies a continuous co-construction of meaning through mutual interaction and perspective taking. However, if there are constraining boundary conditions to these circular processes, then the co-construction of meaning will be disturbed and mutual understanding will fail. Such is the case, for example, when one of the partners is deaf, or does not understand the other's language or cultural background. It is well known that these are typical conditions which in vulnerable persons may lead to suspicion, paranoid ideation and finally to delusions of persecution – termed "paranoia of the hard-of-hearing" (5) or "paranoia of immigrants" (6-8). In these cases, adequate understanding of verbal utterances is compromised, leading to a disturbance of the circles of social interaction and perception.

With some modifications, this description applies to schizophrenic delusions as well. In the prodromal stages of the psychosis, the alienation of perception and the resulting loss of familiar significances particularly extend to the social sphere. The faces, the gazes and the behaviour of others become highly ambiguous, and the interactive circles with others are fundamentally disturbed. In the *delusional mood* arising from this ambiguity, the basic trust in others breaks down (9,10). The co-constitution of a shared world fails and is replaced by the new, idiosyncratic coherence of the delusion.

But this does not at all mean that the others are no longer important. On the contrary, now the patient feels being observed by gazes from the background, being spied at from out of anonymous cars, or secretly tested in well-prepared situations. In other words, he takes others' presumed perspectives even excessively (this has been termed "overmentalization", e.g. 11), but in a way that all these perspectives seem to be directed *centripetally towards himself* in a threatening way.

Delusions may thus be described as a *loss of the excentric position*. Deluded patients are able to take the (supposed) perspective of others; what they lack, however, is the independent position from which they could compare and integrate their own and another's point of view, and from which they could also relativize or question their feeling of centrality and reference (being observed, spied at, persecuted, etc.); this independent or "third" position is the excentric position. Thus, delusions result from the failure of co-constituting the world through mutually taking and aligning one's perspectives. "Double bookkeeping" is a possible consequence: the patient's own and the others' point of view are only juxtaposed instead of being integrated.

Another result is the *exclusion of chance* (12). Chance or coincidence normally allows us to neutralize irrelevant elements of a situation by attributing them to a mere contingency, not to another's intention: "this was not meant for me" or "not aimed at me". For the schizophrenic patient, however, the situation is reversed: it is precisely the normally irrelevant and accidental background elements that adopt a meaningful, sinister and threatening character. The deluded person does no longer acknowledge the possibility of chance, and thus refuses to treat the shared situation as an open one. Everything revolves around him.

In sum, delusions may not be sufficiently described as individual false beliefs. Rather, they correspond to an intersubjective situation bereft of the basic trust that could help to restore a consensual understanding of the situation and to co-constitute a shared, commonsensical reality. No matter what their neurobiological presuppositions and neurocognitive components are – no doubt that these are of crucial importance – delusions are not just products of individual brains. Their basis is not a faulty representation of the world, but a failure of enacting a shared world through interaction with others.

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Therapeutic advances for people with delusions will come from greater specification and empirical investigation

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Phenomenological accounts of delusions focus on the experiences of people – not the delusional content but its mode, manner or form. The emphasis on the detailed description and in-depth exploration of how the person experiences the self and the world, at times of disturbance and distress, is important. Phenomenology has much to teach mental health professionals about recognizing and validating patients' anomalous experiences and their emotional impact. Furthermore, Sass and Byrom (1) offer some elegantly formulated ideas about how information is processed by some people with delusions (their "hyposalience hypothesis") and possible links to certain neurocognitive accounts of delusions. But do these ideas point towards therapeutic advances? I do not think so.

There is much cognitive research on delusions which has informed and influenced cognitive behaviour therapy (CBT), but which appears neglected or even misinterpreted by Sass and Byrom. The cognitive approach, in common with these authors, does not view delusions as unitary phenomena, but it differs in that it also tests empirically the hypothesized mechanisms of cause and persistence of different delusion types. The most striking example concerns persecutory delusions, a common, clinically important delusion type. The recent cognitive research on persecutory delusions is not correctly represented by what Sass and Byrom call "the paranoia paradigm", i.e., "the tendency to view literal beliefs about external threat or attack as constituting the prototypical instance of delusion". On the contrary, the purpose is to understand the causal factors implicated in distinct types of delusion and thence to develop targeted interventions (2). Thus, recent research has examined persecutory, grandiose and religious themed delusions to explore hypothesized differences (for example, 3,4).

There is highly replicated evidence, in dozens of independently conducted studies, of reasoning biases in people with delusions, demonstrating, in comparison to control groups, the tendency to gather less information under conditions of uncertainty (or "jumping to conclusions") (see 2,5 for reviews). I agree that it is possible, as Sass and Byrom note, that the "jumping to conclusions" bias is partially reflected in their concept of an "anything goes mentality". Related to, but distinct from "jumping to conclusions" is a limited reflectiveness about one's own reasoning, which we have called poor belief flexibility – a relative incapacity to reflect on one's judgements, to review and reconsider first impressions and to consider alternatives. Recent evidence suggests that this over-reliance on rapid automatic thinking, at the expense of slower reflective thinking – adopting a two process model of reasoning, as in Kahneman's *Thinking, Fast and Slow* (6) – is an important mechanism of persecutory delusion persistence and change. A randomized study with 100 people with schizophrenia spectrum psychosis and paranoid thinking demonstrated that we can help people with persecutory delusions to become aware of thinking fast, and to slow down their thinking, thereby reducing their paranoia; this points the way forward for new therapeutic strategies (7).

It is of note, perhaps contrary to Sass and Byrom's assumption about the role of emotions underpinning grandiosity, that grandiose delusions are even more strongly characterized by the "jumping to conclusions" reasoning bias than are persecutory delusions (3). But this is emphatically not to deny the importance of emotions in both grandiose and persecutory delusions (3). Sass and Byrom are incorrect in asserting that the paranoia paradigm emphasizes only reasoning biases. Cognitive models of delusions are multifactorial, and research has shown how emotional processes are also active as causal mechanisms of persecutory delusions.

Large scale epidemiological research, experiments and interview-based longitudinal studies have investigated social and psychological mechanisms of paranoid thinking and persecutory delusions (for example, 8-10). Emotional processes are clearly important. For example, Wickham et al (10), in a study of 7,000 members of the general public, found that multiple social and economic indices of deprivation predicted the occurrence of paranoia, and that this was partially mediated by measures of interpersonal trust and stress. Another study which followed 300 patients with schizophrenia spectrum psychosis over 12 months showed that a negative self-concept predicted the persistence and severity of persecutory delusions (8). An experimental investigation of how cannabis triggers paranoia showed that anomalies of experience and negative affect are the most likely mechanisms of action in causing paranoia (9).

Studies such as these lead directly to new therapeutic approaches to delusions. It is a travesty to suggest, as do Sass and Byrom, that CBT therapists working with people with delusions would endorse the idea that "proffering counter-evidence [can] really be the true therapeutic element in successful CBT for psychosis". Indeed, this was never the case. Very early, it was recognized that presenting counter-evidence

is a strikingly unproductive way to work with delusions (11). Rather, the therapy has always involved understanding the grounds for the person's belief – the unusual experiences and events underpinning it – while validating and empathizing with emotional distress; and exploring with the patient, collaboratively, alternative possibilities, cognitive, emotional and behavioural, in the light of the person's history and social environment.

More recently, informed by the more precise empirical evidence of mechanisms of specific symptom persistence, whether of reasoning biases, negative affect or negative self-concept, the CBT approach is to work with the process (if you like, with the mode or manner of the thinking rather than the content) and thereby to alleviate the delusion and its accompanying distress and impact on everyday life (2).

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Answering some phenomenal challenges to the prediction error model of delusions

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Delusions are a challenge; a menagerie of odd beliefs with a diverse set of differential diagnoses and candidate pathologies (1). Their phenomenology has led many to deem them un-understandable (2). On the other hand, their susceptibility to treatment with D2 receptor antagonists has led many clinicians and scientists to consider them understood.

Delusions are neither fully understood nor un-understandable. 20-50% of patients have residual delusions even after adequate D2 blockade (3). A recent model challenges the un-understandability conclusion, suggesting a bridging hypothesis that unites neural and experiential aspects of delusions through computational theory (1). That hypothesis involves prediction errors (PEs) – the mismatches between expectation and experience that guide learning, attention, and belief formation and maintenance. If PEs are signaled inappropriately, delusions result (1).

Sass and Byrom (4) highlight some phenomenological challenges to this explanation. Here, I meet those challenges. I will argue that the aberrant PE model can indeed account for some of the more puzzling aspects of delusions, for example the central role of self-experience in delusions, the curious double bookkeeping in which patients may engage, the role of hyposalience (the bizarre as banal), the "anything goes" inferences made by many people with delusions, as well as bizarre delusions that appear to defy understanding.

Sass and Byrom also speculate that the brain default mode network (DMN) may mediate these latter phenomena. I will join them in this speculation, but I will argue that the DMN too is PE driven (5). As such, I will maintain that PE is still a single factor explanation of delusions, even the most bizarre ones.

Sass and Byrom question whether aberrant PE can explain the centrality of self-experience to delusions, as well as some of the contents of delusions related to inflated self-concept or metaphysics. There is a nascent field examining self-representation in the brain (indeed, this circuitry often overlaps with the DMN). I believe we can conceive of healthy self-experience and ipseity disturbance in the context of PE theory.

PE theory posits that the brain builds hierarchical models to predict the causes of its sensory data (6). Any mismatch between prediction and data can have two consequences: a) it is ignored or overridden by prior beliefs (as is the case with optical illusions), or b) it is transmitted up the hierarchy where it updates the top-down prior with new learning (so expectation is different in the future) (6).

The first-person self is perceived as a result of the same hierarchical modeling process. Ultimately it encodes the evidence for (or belief in) the existence of the self in the world – when all is intact, we model ourselves as agents in our world that can act on our environment and, through acting, change the sensory feedback we receive (7). Under this account, ipseity arises when the agent identifies with its model of the world (8). Aberrant PE would lead to the ipseity disturbances that Sass and Byrom outline through a disruption of this self-modeling process. For example, a surprising lack of self-agency experience, due to a deficit in predicting one's intentions, could lead to passivity delusions (1). According to this account, self-experiences, beliefs and delusions arise as the best explanation for the available data incident upon the organism. This explanation overrides other potential explanations in a winner-take-all manner (1).

Sass and Byrom go on to highlight a phenomenon that challenges this winner-take-all notion: double bookkeeping. Here, patients with delusions lack manifest conviction in their beliefs, e.g., claiming that their food is being poisoned, but eating it nevertheless. It seems that people do not always act on their delusions and that they may simultaneously endorse and deny them (9).

A phenomenon from animal conditioning, extinction learning, might be relevant to double bookkeeping (1). Extinction involves new learning, for example to no longer expect reward or electric shock in a previously reinforced situation. There is a transition from expecting a salient event, to no longer expecting it. Patients recovering from their delusions describe a similar duality of belief and disbelief regarding their delusions (10). Under an extinction account of recovery from delusions, new learning (of a non-delusional belief) competes with and overrides the original reinforced situation (the delusion) (1). Extinction learning (of a new belief) is driven by appropriate PE: when the expected event fails to transpire, a negative PE triggers updating of future expectancies (1). Likewise, the relationship between endorsing and rejecting the delusion is modulated by PE; if a surprising salient event occurs (perhaps one that is reminiscent of the delusion), the old belief may be renewed (1). More broadly, in the face of constant aberrant PE (either in terms of magnitude, timing or precision), new belief formation is necessary. If PE signals remain variable, inconsistent, and difficult to accommodate, it is possible that a new causal model is required – that is a new set of causal associations, a new mechanism that might pertain. Thus PE guides the exploration of the space of possible explanatory beliefs (11) until this PE "over beliefs" is minimized by the adoption of a new higher order causal belief (1). Under constant aberrant PE, one can imagine switching back and forth between delusional and non-delusional interpretations (or double bookkeeping) (1).

Relatedly, Sass and Byrom posit that, for patients with delusions, the bizarre can become banal. Indeed, the PE model appreciates and can account for this. In the face of persistent aberrant PE, patients may learn a hyper-prior – *a prior over priors* – that anything is possible, even the surprising experiences and associations on which their delusions are based (11). This hyper-prior, that the world is always surprising, renders subsequent PE experiences expected – unsurprising, banal. This is a potential explanation for delusion maintenance, double bookkeeping (with respect to manifest conviction) and negative symptoms – if goal-directed actions have proven repeatedly ineffectual, why engage in actions at all (12), and if all beliefs lack explanatory adequacy, why bother acting on them or updating them?

Sass and Byrom suggest that PE may account better for non-bizarre delusions (particularly what they call the paranoid type). I suggest instead that the PE model best explains aberrant salience and delusions of reference. However, our empirical data – linking delusion severity to aberrant PE using functional neuroimaging – were gathered from patients with a range of delusion contents (13). They also claim that bizarre delusions (e.g., "I am the right foot of Christ") are more problematic for PE theory. Here, I point to the overlap between causal belief formation, associative learning and propositional cognition; causal representation may involve linguistic expressions like metaphors (14). Bizarre delusions then represent inappropriate use of metaphor in an attempt to establish some intersubjective meaning, albeit futile.

During the formative delusional mood, the world becomes ineffable. Prodromal patients use relative terms (similes) to describe their experiences: "It is *as if* people are actors, walking down the street wearing masks" (15). As these experiences persist, the relative terms subside (people *are* wearing masks, they *are* in disguise); the simile becomes a metaphor as the delusion develops and the metaphor becomes a top-down prior around which perception and cognition are organized.

Delusional priors form as the best way to account for a noisy and uncertain PE. But if they don't accommodate this PE, the PE will eventually be disregarded and won't update the prior (16). However, the prior will be engaged with, reactivated and therefore strengthened (1). Similar so-called *backfire effects* have been observed with political beliefs (17). They relate to the process of memory reconsolidation, through which memories are reactivated, updated and consolidated once more (1). Aberrant PE may drive inappropriate reactivation, rumination upon and strengthening of delusional priors (1). This ruminative engagement with delusional priors may also be a mechanism through which simile becomes metaphor in bizarre delusions.

Such rumination engages autobiographical memory (perhaps a contributor to ipseity) and the DMN circuitry (18). Sass and Byrom point out that delusion severity has been related to the inappropriate DMN engagement, perhaps as a result of its unconstrained operation in the absence of control from dorsolateral prefrontal

cortex (DLPFC) (19). They argue that DMN responses have been related to self-processing and so the DMN represents a neural locus for ipseity and its disturbance in individuals with delusions. I urge caution in ascribing any function, particularly one as multifaceted as self-processing, to one set of regions.

This problem is further compounded by the challenges of inferring the precise function of DMN (since, by definition, it is engaged when subjects are disengaged, any inferences about its function cannot be corroborated by behavioral data). However, let's assume that DMN is involved in autobiographical processing (i.e., it contributes to ipseity) and that its activity is usually anti-correlated with DLPFC (19). My work has shown that, during causal belief formation, the DLPFC signals an explanatory gap – or PE (1). Others have suggested that the DMN may generate a narrative (possibly autobiographical) to explain such PEs (5).

It is possible then that ipseity may be perturbed through defective engagement of DLPFC, DMN or a faulty interaction between them. Future work should identify the relationship between PE and explanation, DLPFC and DMN function. Their usual anti-correlation is disrupted in psychotic states (19), but the specifics of their interaction in the genesis of experiences, beliefs and delusions is deserving of further scrutiny. Nevertheless, it is possible to explain the relationship between DMN and delusions in the PE framework.

Finally, Sass and Byrom express concern that belief formation in the PE model involves a conscious deliberative process that is cold and logical. This is not the case. All but the highest levels of the hierarchical generative model on which minimal self and delusion formation are based are unavailable to conscious awareness (8). We are not conscious of processing at lower levels of the hierarchy (below narrative self and first person perspective) and so beliefs and delusions form outside of conscious awareness.

Admittedly, our investigations so far have lacked an affective component (note, however, our work on the role of distress in PE signaling and delusion-like ideation (20)). A recent review of the dys-interaction between cognition and emotion in studies of schizophrenia highlighted the role of affect in generating aberrant salience. Across studies, neural and behavioral responses to affectively salient events were attenuated and neutral events garnered excessive affectivity – often these responses correlated with delusion severity (21).

In summary, Sass and Byrom highlight the importance of phenomenological data in generating an explanation of delusions. The PE theory likewise focuses on relating the experiences that characterize delusions to their underlying brain mechanisms (1). The devil though is in the details, and I trust that, by elaborating some PE theory details, I have answered some of the challenges leveled by Sass and Byrom.

It seems that ipseity and PE models are broadly consilient, but concerned with different levels of explanation (22). It is important that we capitalize on this consilience rather than focusing on prioritizing one level of explanation over the others.

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Are the neurocognitive correlates of subtle subjective symptoms the way forward in psychiatry?

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In their thoughtful overview, Sass and Byrom (1) correlate three levels of description: the subjective experience of the patient as understood by a third person (phenomenology), cognitive models and neuroscience. In particular, they link two diverging models with each other, i.e., selected phenomenological accounts of delusions and their potential underlying neurocognitive explications. They identify correlations between the two models and crystallize neglected areas in neurocognitive accounts, filling them with phenomenological notions. Basically, they argue to look for fine grained, subjective symptoms – beyond structured interviews and DSM/ICD criteria – and to relate them to neurocognitive data.

The authors' ambition is to find a neuroscientific explanation of subjective experiences. However, neuroscience should not be a validator for phenomenology, as they are two different realms of description, which should inform each other. There is of course a fundamental "explanatory gap". The subjective consciousness (first person perspective) has to be translated by the patient into a second person "output", usually verbal and non-verbal; this has to be understood by the interviewer and then related to brain states (third person perspective). The mind-body relation is a yet unresolved philosophical question; therefore we can only correlate such levels of descriptions, but we cannot explain them with one another.

Correlating symptoms with brain states has already been successfully achieved by a neuroimaging "symptom catching" approach, mainly for auditory hallucinations and formal thought disorder. In the beginning, cruder syndromes have been related to brain activation (2,3), while recently a more fine grained and subjective psychopathology has been applied (4,5).

In the article, highly selected phenomenological ideas (models) are correlated with current neuroscience models. Since there is not much replicated data on the neurobiology of delusions, Sass and Byrom's account is rather a comparison of models. Ideally, one would have a phenomenologically derived symptom or experience and relate this to empirical data, rather than comparing models with each other. More empirically testable predictions from phenomenology would be welcome.

However, this begs the question of which among the many phenomenological accounts (Sass and Byrom only discuss a few) should be translated into experiments and tested. For current neuroscientific data acquisition, a fluctuating phenomenon/symptom is usually considered, and the patient is investigated experimentally at two or more points in time, with symptom severity being correlated with cognitive measures and/or brain states. This methodological constraint vastly reduces the number of phenomena possibly investigated.

A further current problem is that the conception of our patients' inner lives has been oversimplified by the operationalized diagnostic approaches. This oversimplification has been accompanied by a reliance on methodologies that are unable to capture the delicate forms of human experience and expression (6). If the cognitive scientist wants to base experiments on phenomenological notions, he or she must be deeply familiar with the philosophical-phenomenological literature. This needs thorough reading and understanding of the ideas, which are currently marginalized. Many French and German texts have not been translated into English and are therefore inaccessible to a wider international audience. For example, Sass and Byrom discuss concepts by K. Conrad, but another important phenomenological contribution on chronic, negative symptoms stems from W. Blankenburg (7), both from Marburg. Their two main books have equally not been translated into English.

The clinician should be familiar with the rich descriptive and hermeneutic tradition of psychiatry. We only see in our patients what we know. There are other levels for the explanation of experiences than cognitive psychology and neuroscience, and a deep understanding of the patient's world is interesting and therapeutic in itself. A phenomenologically informed systems neuroscience, integrating environmental, genetic, molecular and brain imaging data in the same patient across his life, will eventually explain the etiology and pathophysiology of mental disorders. It can, however, not replace an interpersonally shared understanding of the patient's inner life as a humane value and source of content in itself.

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Phenomenology *is* Bayesian in its application to delusions

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Sass and Byrom (1) argue that phenomenology "expands the range of testable hypotheses". This resonates with our view that phenomenology "leads to neurobiological hypotheses, which can be tested experimentally" (2,3). It is also a welcome modification of Sass' proposal (4) that phenomenology "serves an explanatory function". If phenomenology "explains" schizophrenia by proposing its core essence as a disturbance of "hyperreflexivity/ipseity" (4), it claims knowledge about causal relationships without recourse to testing hypotheses about mechanism.

The authors see a conflict between "enactive" or "embodied" approaches to cognition and "more intellectualistic sounding" prediction-error formulation. We suggest that this apparent conflict is related to a misunderstanding of the term *beliefs* in predictive coding accounts. In current accounts of Bayesian hierarchical predictive coding, a belief is considered merely a probability distribution over some unknown state and may or may not be consciously accessible (5). A central claim of hierarchical predictive coding models is that such beliefs are fundamentally embodied even at the lowest levels of sensory processing, clearly not implying intellectual conjecture and refutation. Accordingly, studies of patients with schizophrenia point to an alteration of predictive mechanisms at low levels of sensory processing. Behavioral and functional neuroimaging studies of illusory visual perception in schizophrenia patients have suggested impaired predictive mechanisms in early visual cortex (e.g., 6,7). Similarly, mismatch-negativity (MMN), an electrophysiological signal that is thought to reflect the automatic registration of irregularities in sensory input, is reduced in patients with schizophrenia (8). The empirical evidence for altered predictive coding seems to contradict the authors' assumption that the predictive mechanisms involved in delusion formation/maintenance necessarily implicate, or are limited to, cognitive or "intellectualistic" processes.

Furthermore, the authors suggest that the exaggerated prediction-error signaling giving rise to *hyper*salience does not account for *hypo*salience and an associated "anything-goes" attitude, which they propose may be due to a dysfunction in the default-mode network. Apart from possible problems with "reverse inference", we question the assertion that hyposalience as described by the authors is incompatible with the notion of prediction-error dysfunction. To the contrary, predictive coding accounts actually predict that the proposed exaggerated prediction-error signaling (or imbalance in the precision of prediction errors and prior beliefs) (5) results in an impaired distinction between normally expected and unexpected events. This is exemplified by reduced MMN amplitude in schizophrenia conceptualized as a consequence of altered prediction-error signaling. In this context, attenuated mismatch responses in schizophrenia patients may actually not reflect the failure to register surprising events, but rather the fact that each event is surprising (5,7). Hyper- and hyposalience are two sides of the same coin, accounted for by a single factor, prediction-error dysfunction (9).

This is supported by Heidelberg psychiatrist Mayer-Gross' (1932) observation of reduced anticipatory expectation in the "self disturbances", due to the ongoing "interruption" of current goal-processing by the "made" or influenced perceptions, movements, thoughts, etc., which characterize those disturbances (10). There is only the compelling sensory evidence of *now*: "no temporal order prevails, each sensory impression is equally valued, replacing its predecessor". This reduction in top-down, embodied perceptual expectation in the "self disturbances" observed by Mayer-Gross anticipates the predictive coding account of attenuation of visual illusions (e.g., the hollow-mask illusion) in schizophrenia and how this relates to delusions and related symptoms (as discussed by Corlett, Fletcher and Frith, and others).

The phenomenological psychiatrist Binswanger also described the self in schizophrenia as captive in the present moment in a "temporal shrinking" of past and future which resembles dreaming (11). In his fiction, Kafka depicts the reduced expectation in dreamlike-hypnagogic experiences, where protagonists report "expecting" the very events that "surprise" them (12). This is not "bizarre-as-banal", but *the absence of banal altogether*. It is also not "anything-goes", but can be formalized in the Bayesian hierarchy as outlined above. Similarly, Binswanger

describes a "monotonous" spreading of the delusion to the entire perceptual field in terms of a "loosening" of context from prior learning (2,11).

Sass and Byrom's language suggests that "phenomenology" does the work of description and inference (e.g., "phenomenology is acutely sensitive", "phenomenology is cautious"). Such phrasing may lead to the mistaken assumption that phenomenology is a body of *finalized* results articulated by one individual or group, rather than a rigorous method, which includes an ongoing process of dialogue, refinement, and consensus.

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Phenomenological and neurocognitive perspectives on polythematic and monothematic delusions

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Sass and Byrom (1) end their paper by advising us to doubt the wisdom of viewing delusion as a unitary phenomenon. I share their view. We must make distinctions here. And as far as the phenomenology of delusion is concerned, the most important distinction is between polythematic and monothematic delusional conditions (2,3) – critical here because the various phenomenological features of delusion that Sass and Byrom discuss are characteristic of polythematic delusion, but not of monothematic delusion.

In polythematic delusional conditions, the patient expresses delusional beliefs about a wide variety of unrelated topics. For example, amongst the beliefs expressed by P. Schreber were that "nerves" and "rays" were taking over his soul, that he changed into a woman, and that he was omnipotent, omniscient and even omnipresent (4). And amongst the beliefs expressed by the Nobel Laureate J. Nash, diagnosed with schizophrenia, were that he would become Emperor of Antarctica, that he was the left foot of God on Earth, and that his name was really Johann von Nassau (5).

In contrast, in monothematic delusional conditions, the patient expresses only a single delusional belief concerning a single topic. Numerous different monothematic delusions have been described in the literature. Eight of these monothematic delusions (6) are: *Capgras delusion* ("one of my closest relatives has been replaced by an impostor") (7-10); *Cotard delusion* ("I am dead") (11,12); *Frégoli delusion* ("I am being followed around by people who are known to me but who are unrecognizable because they are in disguise") (13-16); *mirrored-self misidentification* ("the person I see in the mirror is not me, but some stranger who looks like me") (17); *reduplicative paramnesia for persons* (a stroke patient affirmed both that her husband had died and had been cremated four years earlier (true) and that he was currently a patient on the ward in the same hospital that she was in (not true)) (17); *somatoparaphrenia* (the patient denies ownership of a limb insisting that this limb actually belongs to someone else, such as a relative or the clinical examiner) (18); *delusion of alien control* ("someone else is able to control my actions; I am a puppet and someone else is pulling the strings") (19); *delusion of thought insertion* ("thoughts are put into my mind like 'Kill God'; it's just like my mind is working but it isn't; they come from this chap Chris; they're his thoughts") (20).

Sass and Byrom summarize the phenomenological perspective on delusion as follows: "Phenomenological accounts

of delusional mood/atmosphere discuss loosening of perceptual context, promiscuous linkages between de-contextualized elements, a sense of being at the center of things, and alienating hyperreflexivity. Such a perspective helps to clarify how paranoid, metaphysical, influence-related, bodily, and solipsistic delusions – together with altered experience of self, intersubjectivity, and felt reality – might develop on the basis of overall structural or ontological changes associated with delusional mood and its aftermath". Examples of all of this are seen in patients with polythematic delusional conditions, especially in what they say when describing their experiences, such as Sass and Byrom's quotations from Schreber.

But scrutiny of the (now quite extensive) literature on monothematic delusions such as the eight delusions listed above reveals nothing like this. Such patients do not report anything like, to quote from Sass and Byrom, "feelings of strangeness and tension and of suggestive yet ineffable meaning" or that "something is in the offing" or "a sense of threat and associated anxiety" or "an abnormal, sometimes excruciating sense of meaningfulness" or an experience of the world as "somehow false, inauthentic, or insinuating". These are all part of the phenomenology of polythematic delusion, but they are not part of the phenomenology of monothematic delusion.

As for neurocognitive hypotheses about delusion, we don't know much about how to explain polythematic delusion, but the two-factor theory (21-23) seems to offer a good explanation of the various monothematic delusions. I will illustrate this for the case of Capgras delusion.

Seeing a familiar face normally generates a much larger response of the autonomic system than seeing an unfamiliar face. But not in patients with Capgras delusion: their autonomic responses are no stronger to familiar than unfamiliar faces (24-26). The two-factor theory of monothematic delusion uses this finding thus: "Suppose that as we go about everyday life we use an internal model of the world (27,28) to continuously predict what we will experience next. These predictions will normally be fulfilled, but occasionally not: occasionally *something not predicted by the internal model occurs*. That event indicates that there is something wrong with the database of beliefs that the model uses to predict what will happen next in the world. So the database needs to be fixed (by modifying existing beliefs or adopting new ones) so that it becomes compatible with the unexpected event. Adopting the belief 'This is not my wife' will make the Capgras patient's belief database compatible with the lack of arousal response to the sight of the wife's face" (29; my emphasis).

As the emphasized phrase indicates, this theory proposes that what triggers the search for a new belief (which will become the Capgras delusion) is prediction error: that is Factor 1. But this is not sufficient to bring about Capgras delusion, because patients with frontal ventromedial damage show the same autonomic symptom as Capgras patients, yet are not delusional (30). The idea prompted by the autonomic abnormality ("That's not my wife") ought to be rejected; it instead becomes adopted as a belief because of the presence of Factor 2, which is defective ability to evaluate beliefs, perhaps associated with right dorsolateral prefrontal cortex abnormality (22).

Analogous two-factor explanations have been offered for the other monothematic delusions (6,21-23).

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Age matters in the prevalence and clinical significance of ultra-high-risk for psychosis symptoms and criteria in the general population: findings from the BEAR and BEARS-Kid studies

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Early detection of psychosis is an important topic in psychiatry. Yet, there is limited information on the prevalence and clinical significance of high-risk symptoms in children and adolescents as compared to adults. We examined ultra-high-risk (UHR) symptoms and criteria in a sample of individuals aged 8-40 years from the general population of Canton Bern, Switzerland, enrolled from June 2011 to May 2014. The current presence of attenuated psychotic symptoms (APS) and brief intermittent psychotic symptoms (BLIPS) and the fulfillment of onset/worsening and frequency requirements for these symptoms in UHR criteria were assessed using the Structured Interview for Psychosis Risk Syndromes. Additionally, perceptive and non-perceptive APS were differentiated. Psychosocial functioning and current non-psychotic DSM-IV axis I disorders were also surveyed. Well-trained psychologists performed assessments. Altogether, 9.9% of subjects reported APS and none BLIPS, and 1.3% met all the UHR requirements for APS. APS were related to more current axis I disorders and impaired psychosocial functioning, indicating some clinical significance. A strong age effect was detected around age 16: compared to older individuals, 8-15-year olds reported more perceptive APS, that is, unusual perceptual experiences and attenuated hallucinations. Perceptive APS were generally less related to functional impairment, regardless of age. Conversely, non-perceptive APS were related to low functioning, although this relationship was weaker in those below age 16. Future studies should address the differential effects of perceptive and non-perceptive APS, and their interaction with age, also in terms of conversion to psychosis.

Key words: Psychosis, ultra-high-risk symptoms, attenuated psychotic symptoms, brief intermittent psychotic symptoms, children and adolescents, general population

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Early detection of psychosis has become an important topic in psychiatry. Yet, despite several efforts to define a clinical high risk of developing psychosis, limited attention has been specifically directed towards children and adolescents (<18 years) (1-4). Two early detection approaches, developed and evaluated predominately in adult or mixed-aged samples, currently prevail (3,5): the basic symptom (6) and the ultra-high-risk (UHR) approach (7). The latter mainly relies on attenuated psychotic symptoms (APS), that is, delusional and hallucinatory phenomena in which some insight is still maintained.

Within the debate on the attenuated psychosis syndrome, proposed for inclusion in the DSM-5, concern about pathologization of non-ill behaviors and experiences has been voiced (8). Such a concern might particularly apply to children and adolescents for several reasons. First, conversion rates in help-seeking UHR samples aged 12-18 years were lower than those observed in adult or mixed-age samples (3,4,9,10), which might indicate a lesser predictive accuracy of UHR criteria in this age group (3). Second, though not assessing the UHR criteria with specific instruments, community studies of children and adolescents found high prevalence rates of APS (11-14), particularly hallucinations, with a spontaneous remission in about three quarters of cases (14). Third, the association of both clinician-rated and self-rated APS with poorer socio-occupational functioning and psychiatric morbidity (12,15-17), and thus their clinical significance, seems to increase with age in community and help-seeking samples of children and adolescents, again especially in the case of hallucinatory phenomena. Thus, it has been recently argued that the validity of current risk criteria needs to be examined, and possibly adapted to this segment of the population (1-3,6).

Traditionally, an age threshold of 18 years is applied in psychiatry to distinguish between early and adult onset. However, it is currently unknown whether the postulated decrease in frequency and increase in clinical significance of APS with advancing age follows this traditional threshold, or rather corresponds to the transition from childhood to adolescence, around the age of 13, or from early to late adolescence, around the age of 16.

In this study, we explored the relationship between age and the prevalence and clinical significance of APS in a sample of individuals aged 8-40 years, who were randomly selected from the general population of Canton Bern, Switzerland.

METHODS

Study design and procedure

Stratified sampling by sex (1:1) was used to randomly select potential participants aged 8-17 years (in the Bi-national Evaluation of At-Risk Symptoms in Children and

Adolescents, BEARS-Kid study) or 16-40 years (in the Bern Epidemiology At-Risk, BEAR study) from approximately 384,000 persons of these age groups included in the obligatory population register of Canton Bern, Switzerland.

In the BEARS-Kid study, subjects were assessed face-to-face, while in the BEAR study subjects were evaluated by telephone interviews that were supported by the computer-assisted telephone interviewing technique (18). Prior to the studies, excellent concordance rates (78-100%) were found for the telephone assessments of risk criteria/symptoms as compared to face-to-face assessments (19).

The ethics committee of the University of Bern approved both studies. Participation in the telephone interview was considered as provision of informed consent in the BEAR study. For the BEARS-Kid study, written informed assent/consent was secured from subjects and their parents.

Recruitment and assessments for the BEAR study were conducted over 14 months (from June 2011 to July 2012) and those for the BEARS-Kid study over 33 months (from September 2011 to May 2014).

In both studies, eligibility criteria included appropriate age, main residence in Canton Bern (i.e., a valid address and not being abroad during the assessment period), and an available telephone number. Interviews were discontinued if respondents had a lifetime diagnosis of psychosis or insufficient German, French or English language skills.

In the BEARS-Kid study, the participation rate was 41.5% of eligible children/adolescents. Those who participated did not differ from those who refused to participate in terms of age, gender and nationality. The main reasons for refusal to participate were lack of interest in the topic (49.6%), lack of time (33.8%), excessive length of the interview (16.5%), and expectation of an uncomfortable interview (11.0%). No reason was provided by 10.2% of those who refused to participate.

In the BEAR study, the participation rate was 66.4% of eligible persons. Those who participated did not differ from those who refused to participate in terms of age, gender and nationality. The main reasons for refusal to participate were lack of interest in the topic (52.9%), lack of time (44.5%), expectation of the assessment of too intimate data (15.3%), and excessive length of the interview (13.2%). No reason was provided by 38.9% of those who refused to participate.

Where allowed by the subsample size, each child/adolescent (aged 8-17 years) was randomly matched by gender and highest educational level of parents to each of the four adult age groups (18-19, 20-24, 25-29, and 30-40 years). Our final sample comprised 535 adults and 154 children/adolescents.

Assessments

Assessments were performed by well-trained psychologists. The Structured Interview for Psychosis Risk Syndromes (SIPS, 20) was used to explore the current presence of APS and brief intermittent psychotic symptoms (BLIPS), and the fulfillment of onset/worsening and frequency requirements for these symptoms in UHR criteria. More specifically, the current presence of any APS (any SIPS item from P1 to P5 with a score between 3 and 5) and any BLIPS (any SIPS item from P1 to P5 with a score of 6) was assessed, as well as the fulfillment of the UHR requirements concerning onset/worsening (onset or worsening within the past 12 months for APS; level of psychotic intensity reached within the past 3 months for BLIPS) and frequency (at least weekly presence in the past month for APS; at least several minutes per day at a frequency of at least once per month for BLIPS). Non-perceptive (P1, P2, P3, and P5) and perceptive (P4) APS/BLIPS were also distinguished.

Symptom-independent current global level of psychosocial functioning was estimated using the Social and Occupational Functioning Assessment Scale (SOFAS, 21), in which a score of $\leq$70 was considered indicative of low functioning. The Mini-International Neuropsychiatric Interview (22) and its version for children (23) were used to assess current non-psychotic mental disorders according to DSM-IV criteria.

To ensure excellent data quality, interviewers received an intensive 3-month training prior to the start of both studies. Further, weekly supervision of symptom ratings was provided by two of the authors (F.S.-L. and C.M.), to avoid erroneous rating of vivid imaginations and fantasies or of experiences related to certain states of development as a UHR symptom, particularly within the BEARS-Kid study.

Statistical analyses

Using SPSS 21.0., frequencies and percentages were compared by chi-square tests, and non-normally distributed interval data and ordinal data were evaluated by the Mann-Whitney U tests.

Binary logistic regression analyses using "enter" were performed to assess effects of different age groups (8-12; 13-15; 16-17; 18-19; 25-29; 30-40) on UHR criteria and each of their requirements. The age group with a peak in the onset of first-episode psychosis (20-24 years) served as the reference group.

Logistic regression analyses were also used to assess the effects of UHR requirements and their interaction with age on low psychosocial functioning, and on the presence of any axis I disorder. To evaluate the potential additional effects of an age $\times$ requirement interaction, both the respective UHR requirements and their interaction with age were entered as independent variables, and the interaction with age was considered as relevant when both backward and forward logistic regression analyses equally selected the interaction term as a predictor. We expected small numbers of low functioning and axis I disorders per age group; therefore, age, rather than age group, was entered in the interaction analyses. Throughout, the goodness-of-fit (GoF) was estimated by the Omnibus test.

Table 1 Socio-demographic and clinical characteristics of subjects with and without ultra-high-risk (UHR) symptoms

	At least one UHR symptom		Total	
	Yes (N=68; 9.9%)	No (N=621; 90.1%)	(N=689)	Statistics
Male, n (%)	26 (38.2)	270 (43.5)	296 (43.0)	$\chi^2_{(1)}=0.69$, p=0.407, V=0.032
Swiss nationality, n (%)	58 (85.3)	576 (92.8)	634 (92.0)	$\chi^2_{(1)}=4.64$, p=0.031, V=0.082
Highest ISCED score of parents, median (quartiles)	3 (3-5)	3.5 (3-5)	3 (3-5)	U=18354.0, p=0.059, r=0.072
Age, median (quartiles)	21.4 (16.1-28.4)	23.5 (19.0-29.6)	23.3 (18.5-29.5)	U=17920.5, p=0.040, r=0.078
Age group, n (%)				$\chi^2_{(6)}=15.6$x, p=0.016, V=0.151
8-12 years (n=45)	10 (22.2)	35 (77.8)	45 (6.6)	
13-15 years (n=31)	7 (22.6)	24 (77.4)	31 (4.6)	
16-17 years (n=78)	8 (10.3)	70 (89.7)	78 (11.5)	
18-19 years (n=81)	6 (7.4)	75 (92.6)	81 (11.9)	
20-24 years (n=155)	12 (7.7)	143 (92.3)	155 (22.2)	
25-29 years (n=144)	11 (7.6)	133 (92.4)	144 (21.1)	
30-40 years (n=155)	14 (9.0)	141 (91.0)	155 (22.2)	
Any current axis I diagnosis, n (%)	26 (38.2)	68 (11.0)	94 (13.6)	$\chi^2_{(1)}=38.73$, p<0.001, V=0.237
First-degree relative with psychosis, n (%)	0	6 (1.0)	6 (0.9)	$\chi^2_{(1)}=0.66$, p=0.415, V=0.031
SOFAS ≤ 70, n (%)	12 (17.6)	13 (2.1)	25 (3.6)	$\chi^2_{(1)}=42.40$, p<0.001, V=0.248

DSM-IV axis I diagnoses: n=57 (8.3%) mood disorders, mainly depression (n=28, 4.1%); n=34 (4.9%) anxiety disorders; n=6 (0.9%) obsessive-compulsive disorder; n=13 (1.9%) eating disorders; n=9 (1.3%) somatization disorders; only assessed in participants of the BEARS-Kid study (n=119): n=4 (3.4%) attention-deficit/hyperactivity disorder; n=1 (0.8%) conduct disorder

ISCED – International Standard Classification of Education, SOFAS – Social and Occupational Functioning Assessment Scale

RESULTS

The current prevalence of any UHR symptom was 9.9%. As no BLIPS were detected, the UHR symptoms were exclusively APS. The prevalence of any perceptive APS was 4.9%; that of any non-perceptive APS was 6.1% (6.0% for any unusual thought content, 3.0% for any persecutory idea, 0.3% for any grandiosity, and 0.7% for any disorganized communication).

Subjects with APS were younger than those without APS, and more likely to have non-Swiss nationality, low psychosocial functioning, and any axis I diagnosis. The related effect sizes were small to medium. We did not find any significant difference in the frequency of APS with regard to participants' gender or highest education of their parents (Table 1).

In logistic regression analyses, the age group reliably distinguished between those with and without APS (GoF: $\chi^2_{(6)}=12.7$, p=0.049). Compared to persons aged 20-24 years, those aged 8-12 and 13-15 years were more likely to report APS, while all other age groups (i.e., 16-17, 18-19, 25-29, 30-40) were not (Table 2).

The model became even more significant (GoF: $\chi^2_{(6)}=27.0$, p<0.001) when only perceptive APS were considered. Odds ratios in subjects aged 8-12 and 13-15 increased while, again, no effect emerged in the adult age groups and in the 16-17-year olds. Conversely, when only non-perceptive APS were considered, the model was non-significant (GoF: $\chi^2_{(6)}=5.4$, p=0.490), indicating that persons across all age groups were equally likely to report non-perceptive APS (Table 2).

When the UHR onset/worsening requirement was considered, the age effects on the prevalence of APS increased (GoF: $\chi^2_{(6)}=34.5$, p<0.001). Again, only persons aged 8-12 and 13-15 years were more likely to fulfill the requirement, as compared to the 20-24-year-olds. Separate analyses of the onset/worsening requirement for perceptive and non-perceptive APS again showed a stronger effect (GoF: $\chi^2_{(6)}=36.5$, p<0.001) of perceptive APS in persons aged 8-12 and 13-15 years, while an age effect for non-perceptive APS (GoF: $\chi^2_{(6)}=6.3$, p=0.389) was not observed (Table 2).

When the UHR frequency requirement was considered, age effects declined to a statistical trend level (GoF: $\chi^2_{(6)}=11.6$, p=0.071), where only persons aged 8-12 were significantly more likely to fulfill the requirement as compared to persons aged 20-24. Again, this age effect was maintained and even intensified for perceptive APS (GoF: $\chi^2_{(6)}=21.9$, p=0.001), while it was missing for non-perceptive APS ($\chi^2_{(6)}=7.5$, p=0.277) (Table 2).

Nine persons (1.3%) fulfilled all the UHR requirements for APS (7 for perceptive and 2 for non-perceptive APS). Only persons aged 8-12 were more likely to meet all the requirements compared to those aged 20-24 (GoF: $\chi^2_{(6)}=22.0$, p=0.001) (Table 3). Due to the small sample size, no separate analyses were performed for perceptive and non-perceptive APS.

Table 2 Effects of age on prevalence and UHR onset/worsening and frequency requirements for APS

		Effect on APS prevalence (irrespective of other UHR requirements)						Effect on APS prevalence (considering the onset/worsening but not the frequency requirement)						Effect on APS prevalence (considering the frequency but not the onset/worsening requirement)					
		β	SE	Wald (df=1)	p	Exp (β)	95% CI	β	SE	Wald (df=1)	p	Exp (β)	95% CI	β	SE	Wald (df=1)	p	Exp (β)	95% CI
Any APS	**8-12 yrs.**	**1.23**	**0.47**	**6.86**	**0.009**	**3.41**	**1.36-8.52**	**2.25**	**0.63**	**12.74**	**0.000**	**9.44**	**2.75-32.37**	**1.34**	**0.61**	**4.91**	**0.027**	**3.82**	**1.17-12.50**
	13-15 yrs.	**1.25**	**0.52**	**5.65**	**0.017**	**3.48**	**1.22-9.71**	**1.98**	**0.70**	**7.94**	**0.005**	**7.26**	**1.83-28.83**	0.98	0.74	1.77	0.184	2.66	0.63-11.27
	16-17 yrs.	0.31	0.48	0.42	0.519	1.36	0.53-3.48	0.41	0.78	0.28	0.596	1.51	0.33-6.92	−0.01	0.72	0.00	0.993	0.99	0.24-4.08
	18-19 yrs.	−0.05	0.52	0.01	0.927	0.95	0.34-2.64	−0.05	0.88	0.00	0.959	0.96	0.17-5.33	−0.46	0.83	0.31	0.575	0.63	0.12-3.19
	25-29 yrs.	−0.02	0.43	0.00	0.973	0.99	0.42-2.31	−0.63	0.87	0.52	0.470	0.53	0.10-2.95	−0.64	0.72	0.79	0.373	0.53	0.13-2.15
	30-40 yrs.	0.17	0.41	0.17	0.682	1.18	0.53-2.65	−1.41	1.12	1.57	0.211	0.25	0.03-2.22	0.54	0.53	1.03	0.309	1.71	0.61-4.83
Any perceptive APS	**8-12 yrs.**	**2.02**	**0.59**	**11.75**	**0.001**	**7.50**	**2.37-23.74**	**2.47**	**0.84**	**8.70**	**0.003**	**11.77**	**2.29-60.58**	**2.47**	**0.84**	**8.70**	**0.003**	**11.77**	**2.29-60.58**
	13-15 yrs.	**1.97**	**0.64**	**9.43**	**0.002**	**7.20**	**2.04-25.39**	**2.43**	**0.89**	**7.43**	**0.006**	**11.33**	**1.98-64.96**	0.94	1.24	0.57	0.451	2.55	0.22-29.03
	16-17 yrs.	−0.24	0.85	0.08	0.781	0.79	0.15-4.16	−16.87	4551.0	0.00	0.997	0.00	0.00	−0.01	1.23	0.00	0.996	0.99	0.09-11.13
	18-19 yrs.	0.44	0.69	0.42	0.517	1.56	0.41-5.97	−16.87	4465.9	0.00	0.997	0.00	0.00	−0.05	1.23	0.00	0.971	0.96	0.09-10.71
	25-29 yrs.	−0.15	0.68	0.05	0.821	0.86	0.23-3.26	−0.63	1.23	0.26	0.611	0.54	0.05-5.96	−16.87	3349.4	0.00	0.996	0.00	0.00
	30-40 yrs.	−0.23	0.68	0.11	0.740	0.80	0.21-3.02	−16.87	3228.4	0.00	0.996	0.00	0.00	−0.70	1.23	0.32	0.569	0.50	0.05-5.54
Any non-perceptive APS	8-12 yrs.	−0.16	0.81	0.034	0.846	0.86	0.18-4.18	−16.87	5991.6	0.00	0.998	0.00	0.00	−0.38	1.11	0.12	0.730	0.68	0.08-5.99
	13-15 yrs.	0.68	0.71	0.92	0.338	1.97	0.49-7.88	−16.87	7218.9	0.00	0.998	0.00	0.00	1.17	0.76	2.37	0.124	3.21	0.73-14.22
	16-17 yrs.	0.43	0.56	0.58	0.446	1.53	0.51-4.58	−0.01	1.23	0.00	0.996	0.99	0.09-11.13	−0.94	1.10	0.73	0.393	0.39	0.05-3.39
	18-19 yrs.	−0.35	0.69	0.25	0.616	0.71	0.18-2.74	−0.05	1.23	0.00	0.971	0.96	0.09-10.71	−0.28	0.85	0.11	0.746	0.76	0.14-4.00
	25-29 yrs.	−0.23	0.55	0.17	0.685	0.80	0.27-2.36	−16.87	3349.4	0.00	0.996	0.00	0.00	−0.45	0.74	0.37	0.544	0.64	0.15-2.72
	30-40 yrs.	0.60	0.46	1.72	0.190	1.82	0.74-4.48	−16.87	3228.4	0.00	0.996	0.00	0.00	0.62	0.57	1.16	0.281	1.85	0.61-5.65

Binary logistic regression analyses with method "enter" and 20-24-year olds as reference age group. Significant predictors are in bold type
UHR – ultra-high-risk, APS – attenuated psychotic symptoms

Table 3 Effect of age on current presence of any APS

Age group	β	SE	Wald (df=1)	p	Exp(β)	95% CI
8-12 yrs.	**2.01**	**0.88**	**5.17**	**0.023**	**7.46**	**1.32-42.18**
13-15 yrs.	1.66	1.02	2.66	0.103	5.28	0.71-38.97
16-17 yrs.	−16.87	4550.96	0.00	0.997	0.00	0.00
18-19 yrs.	−0.05	1.23	0.00	0.971	0.96	0.09-10.71
25-29 yrs.	−16.87	3349.41	0.00	0.996	0.00	0.00
30-40 yrs.	−16.87	3228.38	0.00	0.996	0.00	0.00

Binary logistic regression analysis with method "enter" and 20-24-year olds as reference age group. Significant predictors are in bold type
APS – attenuated psychotic symptoms

Low psychosocial functioning was predicted by all APS requirements, and APS frequency was found to be the strongest predictor (Table 4). For perceptive APS, the effect on functioning was less pronounced: only sufficiently frequent APS predicted low functioning. On the contrary, all non-perceptive APS requirements were highly predictive of low functioning (Table 4).

Significant age × requirement interactions in the prediction of low psychosocial functioning indicated that APS occurrence and recency were more predictive of low functioning in the older sample, but frequency requirements were not (Table 4). A similar, slightly stronger effect was detected for non-perceptive APS onset requirement (Table 4). On the contrary, all interactions between age and perceptive APS requirements on low psychosocial functioning were non-significant (Table 4).

Psychiatric morbidity was predicted by all APS requirements (Table 5). Again, APS frequency was found to be the strongest predictor. For both perceptive and non-perceptive APS, only occurrence and frequency were predictive, but not the onset/worsening requirement (Table 5). An interaction with age was detected only for the onset/worsening requirement (Table 5), indicating that recent onset or worsening of APS had a stronger association with psychiatric morbidity in the older age group. No specific age-interaction effects were detected regarding the impact of psychiatric morbidity on perceptive or non-perceptive APS (Table 5).

The age effect on the occurrence of APS, particularly perceptive APS, indicated an age threshold around age 16. To confirm this, and to test for additional age effects within the two age groups below (8-15) and above (16-40) this cut-off, we re-ran logistic regression analyses on occurrence, onset and frequency requirements, as well as the APS criterion separately, within these two age groups. In support of a single 16-year threshold, all results were non-significant.

Next, we used the 16-year cut-off to re-explore the interactions between the two age groups and APS requirements on psychosocial functioning and axis I diagnosis. Results supported the age threshold with regard to the interaction effects on psychosocial functioning. The interactions again indicated a stronger association between lower psychosocial functioning and presence (GoF: $\chi^2_{(1)}=27.1$, $p<0.001$) or recency of APS (GoF: $\chi^2_{(1)}=7.4$, $p=0.007$), in particular non-perceptive ones (GoF: $\chi^2_{(1)}=8.0$, $p=0.005$) and in the older group (as indicated by significant standardized residuals in chi-square tests, i.e., 3.7-6.4). The age × onset interaction effect on psychiatric morbidity, however, was not replicated by using the 16-year cut-off.

DISCUSSION

Within our community sample of never-psychotic 8-40-year olds, 9.9% reported UHR symptoms in the clinical interviews carried out by well-trained clinical psychologists, using the SIPS. UHR symptoms were exclusively rated as APS. All the UHR requirements for APS were fulfilled by only 1.3% of the sample, or 13.2% of those with APS. Indicating some clinical significance of APS, their presence was related to more frequent current DSM-IV axis I disorders and/or functional impairment.

The results strongly indicated an age effect, with a significant shift in both prevalence and clinical significance of APS and their UHR requirements from early to late adolescence, i.e., around age 16 years. The age effect on prevalence was exclusive to perceptive APS, i.e., unusual perceptual experiences and attenuated hallucinations. As compared to 16-40-year olds, subjects aged 8-15 were more likely to report perceptive APS, and were more likely to do so with an onset or worsening of symptoms within the year prior to the interview. This is in line with earlier studies on hallucinations in community samples of children/adolescents, which indicated a high prevalence, though little persistence over time, particularly of infrequent, less than weekly hallucinations (24).

With regard to clinical significance, perceptive APS were mainly unrelated to low current psychosocial functioning, except when frequent. This pattern persisted when age was considered. Actually, although functional impairment has been related to clinician-assessed APS-like symptoms in other samples of children and adolescents (12,25,26), those studies did not separately examine perceptive and non-perceptive symptoms. Indeed, we found a positive association between the occurrence of any APS and low psychosocial functioning, increasing with age. Yet, this association, particularly in older age groups, relied heavily on non-perceptive APS, mainly unusual thought content or persecutory ideas. These consistent, though different, interaction patterns of perceptive and non-perceptive APS with functional deficits and age suggest that attenuated delusional ideas, but not attenuated hallucinatory experiences, co-occur with functional deficits. It also indicates that this co-occurrence is more likely when the onset or worsening of attenuated delusional ideas is recent, or their frequency high, and when the person has already entered late adolescence or adulthood.

Table 4 Prediction of low psychosocial functioning (SOFAS score ≤ 70) by APS requirements and estimation of interaction with age effects

Prediction by APS requirements*	β	SE	Wald (df=1)	p	Exp (β)	95% CI	Omnibus test	Interaction with age effects**	β	SE	Wald (df=1)	p	Exp (β)	95% CI	Omnibus test
Occurrence of APS irrespective of onset/worsening and frequency requirements															
Any APS	**2.31**	**0.42**	**29.55**	**<0.001**	**10.02**	**4.37-23.01**	**$\chi^2_{(1)}$=42.4, p<0.001**	Any APS × age	**0.09**	**0.02**	**33.99**	**<0.001**	**1.09**	**1.06-1.12**	**$\chi^2_{(1)}$=27.4, p<0.001**
Any perceptive APS	1.02	0.64	2.541	0.111	2.78	0.79-9.81	$\chi^2_{(1)}$=2.0, p=0.154	Only perceptive APS × age	No interaction effect						
Any non-perceptive APS	**2.58**	**0.45**	**33.31**	**<0.001**	**13.17**	**5.49-31.60**	**$\chi^2_{(1)}$=52.1, p<0.001**	Only non-perceptive APS × age	No stable model						
Occurrence of APS considering the onset/worsening but not the frequency requirement															
Any APS	**1.72**	**0.59**	**8.54**	**0.003**	**5.56**	**1.76-17.57**	**$\chi^2_{(1)}$=6.3, p=0.012**	Any APS × age	**0.10**	**0.03**	**11.94**	**0.001**	**1.10**	**1.04-1.16**	**$\chi^2_{(1)}$=8.8, p=0.003**
Any perceptive APS	0.82	1.06	0.59	0.441	2.26	0.28-18.13	$\chi^2_{(1)}$=0.5, p=0.488	Only perceptive APS × age	No interaction effect						
Any non-perceptive APS	**3.36**	**1.02**	**10.80**	**0.001**	**28.78**	**3.88-213.44**	**$\chi^2_{(1)}$=8.0, p=0.05**	Only non-perceptive APS × age	**0.17**	**0.05**	**10.75**	**0.001**	**1.18**	**1.07-1.30**	**$\chi^2_{(1)}$=8.4, p=0.004**
Occurrence of APS considering the frequency but not the onset/worsening requirement															
Any APS	**2.92**	**0.46**	**40.33**	**<0.001**	**18.58**	**7.54-45.78**	**$\chi^2_{(1)}$=31.4, p<0.001**	Any APS × age	No stable model						
Any perceptive APS	**1.74**	**0.80**	**4.68**	**0.030**	**5.69**	**1.18-27.45**	**$\chi^2_{(1)}$=3.3, p=0.069**	Only perceptive APS × age	No interaction effect						
Any non-perceptive APS	**3.19**	**0.49**	**42.14**	**<0.001**	**24.34**	**9.28-63.81**	**$\chi^2_{(1)}$=32.3, p<0.001**	Only non-perceptive APS × age	No stable model						

*Binary logistic regression analyses with method "enter", ** binary logistic regression analyses with method "backward" and "forward" using the respective requirement and its interaction with age as independent variables. Significant predictors are in bold type

APS – attenuated psychotic symptoms, SOFAS – Social and Occupational Functioning Assessment Scale

Table 5 Prediction of presence of any axis I disorder by APS requirements and estimation of interaction with age effects

Prediction by APS requirements*	β	SE	Wald (df=1)	p	Exp (β)	95% CI	Omnibus test	Interaction with age effects**	β	SE	Wald (df=1)	p	Exp (β)	95% CI	Omnibus test
Occurrence of APS irrespective of onset/worsening and frequency requirements															
Any APS	**1.62**	**0.28**	**33.16**	**<0.001**	**5.03**	**2.90-8.73**	**$\chi^2_{(1)}$=29.5, p<0.001**	Any APS × age			No interaction effect				
Any perceptive APS	**1.48**	**0.37**	**15.77**	**<0.001**	**4.39**	**2.12-9.10**	**$\chi^2_{(1)}$=13.6, p<0.001**	Only perceptive APS × age			No stable model				
Any non-perceptive APS	**1.50**	**0.34**	**19.52**	**<0.001**	**4.49**	**2.31-8.74**	**$\chi^2_{(1)}$=16.98, p=0.044**	Only non-perceptive APS × age			No interaction effect				
Occurrence of APS considering the onset/worsening but not the frequency requirement															
Any APS	**1.80**	**0.41**	**19.29**	**<0.001**	**6.07**	**2.72-13.58**	**$\chi^2_{(1)}$=17.0, p<0.001**	Any APS × age	**0.10**	**0.02**	**18.97**	**<0.001**	**1.11**	**1.06-1.16**	**$\chi^2_{(1)}$=19.2, p<0.001**
Any perceptive APS	1.06	0.61	3.02	0.082	2.89	0.87-9.59	$\chi^2_{(1)}$=2.6, p=0.108	Only perceptive APS × age			No interaction effect				
Any non-perceptive APS	1.86	1.01	3.43	0.064	6.45	0.90-46.32	$\chi^2_{(1)}$=3.0, p=0.081	Only non-perceptive APS × age			No interaction effect				
Occurrence of APS considering the frequency but not the onset/worsening requirement															
Any APS	**2.08**	**0.37**	**31.75**	**<0.001**	**7.99**	**3.88-16.46**	**$\chi^2_{(1)}$=28.8, p<0.001**	Any APS × age			No interaction effect				
Any perceptive APS	**1.55**	**0.60**	**6.77**	**0.009**	**4.72**	**1.47-15.19**	**$\chi^2_{(1)}$=5.8, p=0.016**	Only perceptive APS × age			No interaction effect				
Any non-perceptive APS	**2.14**	**0.43**	**25.24**	**<0.001**	**8.52**	**3.69-19.66**	**$\chi^2_{(1)}$=23.2, p<0.001**	Only non-perceptive APS × age			No interaction effect				

*Binary logistic regression analyses with method "enter", ** binary logistic regression analyses with method "backward" and "forward" using the respective requirement and its interaction with age as independent variables. Significant predictors are in bold type
APS – attenuated psychotic symptoms

Compared to the interaction between APS and psychosocial functioning, that between psychiatric morbidity and APS was more general, and not moderated by age, except for the onset/worsening requirement. Thus, the increase in the association between APS-like symptoms and psychiatric morbidity with advancing age, suggested by a descriptive comparison of results of two separate samples of 11-13 and 13-15-year olds (13), was not confirmed in our sample. Only with respect to the onset/worsening requirement, a similar interaction was observed: a recent onset or worsening of APS was more strongly linked to psychiatric morbidity in older age groups. In terms of a schizotypy model (27), this stronger association between recently developed APS and non-psychotic psychiatric morbidity in the older age groups might indicate that APS developing in childhood or adolescence might be subject to a certain mental stabilization and adjustment across early adulthood, being therefore less linked to psychiatric morbidity. Yet, more research is clearly required to examine this interaction and its potential moderators.

As our results might have significant clinical implications, they call for replication in larger samples. In particular, the age groups below age 16 years were rather small in the present study, thus potentially limiting the power of our analyses. A strength of the study, however, was the broad age range, allowing for data-driven comparisons of age effects, rather than comparisons of rates reported in separate samples in the literature. The minimum age of 8 years was chosen because the source monitoring of perception necessary for distinguishing between hallucinations and products of fantasy might not have been completely developed before that age (28). The maximum age of 40 years was chosen on the basis of the highest reported intake age in clinical UHR samples (18). Yet, in particular with regard to the second onset peak of psychosis in women (29,30), possible gender-related age effects on the prevalence and clinical significance of APS in samples older than age 40 still warrant examination. However, our chosen maximum age should sufficiently ensure the absence of brain processes related to old age that might result in APS-like phenomena, possibly not identifiable in telephone interviews.

The participation rate of eligible children/adolescents in the BEARS-Kid study was within the reported range of other epidemiological studies on children and adolescents (30). The participation rate of eligible persons in the BEAR study was excellent (18). Both samples were sufficiently representative of the general population of the Canton Bern, although the eligible BEARS-Kid sample was slightly older (small effect), while the eligible BEAR sample was slightly biased against 26-30-year olds and towards 36-40-year olds (18). However, this bias was unlikely to have influenced our findings, as no age effect within the adult age groups was detected.

One possible limitation in terms of assessments was that interviews were conducted face-to-face in children/adolescents and via telephone in adults. Yet, prior to commencing the study, we had found that both face-to-face and telephone-interviews enabled a reliable assessment of APS across age groups (18,19). Nevertheless, the use of risk criteria identical to those adopted in clinical settings and the assessment of symptoms by an established interview for attenuated and frank psychotic symptoms, conducted by trained and closely supervised clinical psychologists, is a strength that ensured the high quality of the data.

In conclusion, as the early detection of psychosis is increasingly moving into younger age groups, the issue of validity and clinical significance of current UHR symptoms and criteria in children/adolescents is becoming increasingly pressing (1-3,6). Indeed, our findings clearly ask for further studies of APS in relation to different age groups, in order to avoid misinterpretation of their psychopathological nature. Thereby, the higher prevalence of perceptive APS in children and young adolescents below age 16 calls for their re-appraisal in this age group in both the early detection of psychosis and the diagnosis of attenuated psychosis syndrome, if it is introduced into the DSM-5.1.

Of interest for all age groups, perceptive APS seem to be less related to low psychosocial functioning than non-perceptive APS in the general population, unless they are frequent. These findings ask for replication and the differential study of perceptive and non-perceptive APS and their interaction with age, in order to better distinguish ill from non-ill experiences in the general population, and in children and young adolescents in particular.

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5-HTTLPR genotype potentiates the effects of war zone stressors on the emergence of PTSD, depressive and anxiety symptoms in soldiers deployed to Iraq

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Exposure to war zone stressors is common, yet only a minority of soldiers experience clinically meaningful disturbance in psychological function. Identification of biomarkers that predict vulnerability to war zone stressors is critical for developing more effective treatment and prevention strategies not only in soldiers but also in civilians who are exposed to trauma. We investigated the role of the serotonin transporter linked polymorphic region (5-HTTLPR) genotype in predicting the emergence of post-traumatic stress disorder (PTSD), depressive and anxiety symptoms as a function of war zone stressors. A prospective cohort of 133 U.S. Army soldiers with no prior history of deployment to a war zone, who were scheduled to deploy to Iraq, was recruited. Multilevel regression models were used to investigate associations between 5-HTTLPR genotype, level of war zone stressors, and reported symptoms of PTSD, depression and anxiety while deployed to Iraq. Level of war zone stressors was associated with symptoms of PTSD, depression and anxiety. Consistent with its effects on stress responsiveness, 5-HTTLPR genotype moderated the relationship between level of war zone stressors and symptoms of emotional disturbance. Specifically, soldiers carrying one or two low functioning alleles (S or L_G) reported heightened symptoms of PTSD, depression and anxiety in response to increased levels of exposure to war zone stressors, relative to soldiers homozygous for the high functioning allele (L_A). These data suggest that 5-HTTLPR genotype moderates individual sensitivity to war zone stressors and the expression of emotional disturbance including PTSD symptoms. Replication of this association along with identification of other genetic moderators of risk can inform the development of biomarkers that can predict relative resilience vs. vulnerability to stress.

Key words: 5-HTTLPR genotype, war zone stressors, PTSD, depression, anxiety, biomarkers, stress responsiveness

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Although not without controversy (1), there is growing recognition that genetic factors in combination with exposure to stressful and/or life threatening situations contribute to the development of psychiatric disorders, such as post-traumatic stress disorder (PTSD) (2) and depression (3).

After controlling for baseline characteristics, deployed soldiers with exposure to combat stressors are three times more likely to develop PTSD symptoms relative to deployed soldiers with no combat stress exposure (4). However, exposure to war zone stressors does not impact all soldiers similarly. Some soldiers develop moderate to severe anxiety and depression symptoms following war zone stress exposure, whereas others do not (4). Similarly, epidemiologic data indicate that many Americans (60.7%) have been exposed to a traumatic stressor, yet only a small minority (8%) developed PTSD (5). Although a number of risk factors for PTSD and depression have been identified (6), genetic variation is believed to partially explain individual differences that occur in such dysfunctional responses to trauma (7).

Evidence from twin studies involving Vietnam War veterans first indicated that approximately 30% of the variance in PTSD can be attributed to shared genetic variance (8). Similar estimates for the genetic liability to depression and other anxiety disorders have been established (9). Subsequent candidate gene studies have provided limited evidence for specific genetic loci shaping risk for PTSD (10). Several promising gene-by-environment (GxE) interaction findings have recently been reported, involving genetic variants that putatively influence hypothalamic-pituitary-adrenal (HPA) axis function (i.e., FKBP5 and CRHR1) (11), GABA receptor functioning (i.e., GABRA2) (12), and G protein signaling (i.e., RGS2) (13).

Of particular interest in mapping the genetic risk for PTSD are studies of the functional variable number tandem repeat polymorphism in the proximal promoter of the serotonin transporter gene (i.e., the serotonin transporter linked polymorphic region or 5-HTTLPR). This interest reflects the importance of the serotonin transporter in mediating active clearance of extracellular serotonin and thereby influencing the duration and intensity of serotonin signaling. This signaling pathway is an important modulator of a cortico-limbic neural circuitry mediating behavioral and physiologic responses to stress and threat, including trauma (14,15).

The 5-HTTLPR is most commonly represented by two variants: a short (S) allele and a long (L) allele. The presence of one or two short alleles, rather than two copies of the long allele, may be associated with reduced transcriptional efficiency that putatively results in significant decreases (approximately 50%) in serotonin reuptake (16,17). This 5-HTTLPR effect may be modulated by a single nucleotide polymorphism (rs25531) comprised of an adenine (A) to

guanine (G) substitution, most commonly occurring at the sixth nucleotide in the first of two extra 20 to 23 bp repeats of the L allele (18). Importantly, the L allele with guanine at the sixth nucleotide (L_G) exhibits similar reductions in transcriptional activity to the S allele in comparison to the L allele with adenine at the sixth nucleotide (L_A) (19). This has led most to adopt a "triallelic" classification scheme for the 5-HTTLPR, with the following functionally defined alleles: L'=L_A and S'=S, L_G, yielding the following functional genotypes: L'L' (high activity), L'S' (intermediate activity), and S'S' (low activity).

Consistent with the resulting increases in synaptic serotonin (20), the S (or S') allele has been associated with relatively increased neural, behavioral and physiologic reactivity to stress, threat and trauma (21). This profile of heightened sensitivity to environmental challenge translates into a well-documented GxE effect of increased risk for mood and anxiety disorders in the context of stressful life events in carriers of the S allele (3). Stratifying study samples by type of stressor has revealed a significant relationship between 5-HTTLPR genotype and depression for studies of childhood maltreatment, medical conditions, and life stress (21).

Surprisingly, relatively few studies have directly examined the moderating role of the 5-HTTLPR in the emergence of PTSD. Among female undergraduates who varied in their exposure to an on-campus shooting, the S' allele was associated with significantly greater PTSD symptoms 2-4 weeks post-shooting (22). Similarly, the S' allele was associated with increased risk for PTSD in individuals who lacked social support (23) or lived in regions with high unemployment and neighborhood crime (24) in the aftermath of Hurricane Katrina. Further, a cross-sectional study reported that the S allele was associated with increased risk for PTSD in individuals experiencing adult traumatic events and childhood adversity, and especially if they experienced both types of trauma (25). Among refugees from the Rwandan Civil War, the S allele was associated with increased risk for PTSD at relatively low levels of trauma; however, this differential risk for PTSD diminished as trauma exposure increased (26). In contrast, among people exposed to three or more traumas in a large epidemiological sample (N=3,045 adults from Pomerania, Germany), the L' allele was associated with increased risk for PTSD (27).

Here we examine whether 5-HTTLPR genotype interacts with a stressful war zone environment to predict the development of PTSD, anxiety and depression symptoms among soldiers from the U.S. Army deployed to Iraq. The current prospective study is unique in several ways. First, exposure to war zone stressors was assessed during deployment in Iraq via web-based surveys in which soldiers provided monthly reports of recent war zone experiences. Most prior studies have been limited by retrospective recall of traumatic or stressful experiences over long periods of time (28,29). Second, the soldiers in the current study had not previously been deployed to a war zone, which helps minimize heterogeneity of our sample. Third, we rigorously assessed psychopathology at pre-deployment in order to account for its variability prior to exposure to war zone stress. Based on the documented neural, physiologic and behavioral effects of the 5-HTTLPR, we predicted that S' carriers would be at greater risk than L' homozygotes to develop PTSD, depressive and anxiety symptoms in response to increasing levels of exposure to war zone stressors.

METHODS

Participants

Participants were 133 U.S. Army soldiers with no prior war zone experience, who were scheduled to deploy to Iraq within 90 days. The principal investigator and the project director conducted briefing meetings for potential participants from eight combat and two combat support units at Fort Hood Texas. Of the 223 soldiers who attended the group orientation sessions, 184 (82%) provided informed consent and completed an extensive 8-hour pre-deployment assessment at the University of Texas at Austin. Six soldiers were not deployed and one soldier withdrew from the study. Of the 177 deployed soldiers, genetic data were unavailable for 31 soldiers, while 13 soldiers failed to complete any war-zone stress assessments while being deployed. Thus, the final sample included 133 soldiers who provided DNA samples prior to deployment and in-theater reports of war-zone stress experiences.

The study was approved by the Office of Research Support and Compliance at the University of Texas at Austin and the Brooks Army Medical Center Scientific and Human Use Review Committee. All study participants provided informed consent.

Assessments

Prior to deployment, groups of four to six soldiers arrived for study participation by 8.00 a.m., and were monitored by study personnel until dismissal approximately 8 to 9 hours later. After providing informed consent, participants provided a saliva sample for DNA isolation, completed a comprehensive stress risk assessment battery, and were interviewed to assess the presence of DSM-IV diagnoses by the Structured Clinical Interview for DSM-IV (SCID-I, 30).

Soldiers were deployed to Iraq approximately 60 to 90 days after the pre-deployment assessment, and reported war-zone stress experiences during deployment on a monthly basis using the Combat Experiences Log (CEL), a web-based system for prospectively assessing war-zone stress in theater (31). From a list of 18 well-validated war-zone stressors (e.g., received hostile incoming fire, been wounded or injured in combat, received bad news from home), they were asked to indicate stressors they experienced since their most recent in-theater CEL entry (or since

deployment to the combat zone in the event of their very first response to the CEL system). These 18 stressors were drawn from a modified version of the Deployment Risk and Resilience Inventory (32). Further, the CEL allowed soldiers to record up to two unique stressors not covered by the 18 standard stressor items. The number of reported combat stressors was summed for each soldier to estimate the level of war-zone stress exposure for each CEL entry.

PTSD symptoms were assessed using the 4-item PTSD Checklist (PCL-Short) (33). Despite its brevity, the PCL-Short assesses each of the three core PTSD symptom clusters: re-experience (2 items), avoidance (1 item), and hyperarousal (1 item), with a diagnostic accuracy estimate equivalent to that of the original 17-item PCL (33). For the current sample, the internal consistency (Cronbach's alpha) computed from soldiers' first in-theater entry was .79.

In-theater depression symptoms were assessed using the brief 10-item version of the Center for Epidemiologic Studies Depression Scale (CES-D) (34). The CES-D was developed to screen general populations for the presence of depressive symptoms, and thus the content of its items is designed to be understandable and emotionally accessible to all individuals irrespective of their clinical status. Moreover, the CES-D has shown excellent psychometric properties, and has been widely administered in various measurement modes, including web-based assessment (35). The 10-item version is strongly associated with scores from the full 20-item version (kappa=.97, $p<0.001$) (34). For the current sample, the internal consistency computed from soldiers' first in-theater entry was .73.

The CEL also measures anxiety reactions during deployment using 18 items constructed to address common anxiety symptoms across three major domains: cognitive (e.g., fear of losing control), emotional (e.g., feeling scared), and somatic (e.g., tension in muscles). Each symptom was rated on a 5-point scale (1=not at all to 5=extremely). Internal consistency computed from soldiers' first in-theater entry was .92 for the current sample (31).

DNA collection and genotyping

Saliva was collected with the Oragene DNA self-collection kit following the manufacturer's instructions. Participants rubbed their tongues around the inside of their mouth for about 15 sec and then deposited approximately 2 ml of saliva into the collection cup. Participants secured the cup firmly by screwing it clockwise until snug which released a solution from the lower compartment that mixed with the saliva. This started the initial phase of DNA isolation and stabilized the saliva sample for long-term storage at room temperature (36). Saliva samples were shipped to the University of Pittsburgh for DNA extraction and genotyping.

A triplex polymerase chain reaction (PCR) protocol followed by double restriction endonuclease digestion was used to identify the 5-HTTLPR and rs25531 variants: S, L_A and L_G (18). In a total volume of 20 l, 25 ng of genomic DNA were amplified in 1 Multiplex master mix (Qiagen, Valencia, CA) primers at final concentrations of 200 nM. The primer sequences were the following: forward, 5'-TCCTCCGCTTTGGCGCCTCTTCC-3', and reverse, 5'-TGGGGGTTGCAGGGGAGATCCTG-3'. Thermal cycling involved 15 min of initial denaturation at 95°C followed by 35 cycles at 94°C for 30 sec, 62°C for 90 sec, and 72°C for 60 sec. This was followed by thermal cycling at 72°C for 10 min. To distinguish the A/G single nucleotide polymorphism of the rs25531, we extracted 7 ul of the PCR product for digestion by 5 U HpaII (an isoschizomer of MspI) or 10 U MspI, for a total reaction of 17 ul. These were loaded side by side on 2.5-3.0% agarose gel.

These methods produced allele frequencies of S, n=114 (42.86%); L_A, n=143 (53.76%); and L_G, n=9 (3.38%), and a genotype distribution of SS, n=22 (16.54%); SL_G, n=3 (2.26%); L_GL_G, n=0 (0%); SL_A, n=67 (50.38%); L_GL_A, n=6 (4.51%); and L_AL_A, n=35 (26.32%). Genotype distribution of the 5-HTTLPR across all participants was in Hardy-Weinberg equilibrium, χ^2 (3)=0.67, p=0.85. Consistent with previous research (19,37), the S and L_G alleles were treated as functionally equivalent for purposes of analysis, which employed the following genotype groups: L'L'=35, L'S'=73, and S'S'=25.

Statistical analysis

Multilevel, mixed-effects random coefficient regression models (MRMs) were used to analyze the data. Our dependent variables were PTSD symptoms, depressive symptoms and anxiety symptoms (together referred to as war zone stress reactions), measured monthly during deployment. In order to examine the relation between stressors and war zone stress reactions over and above the mutual effect of "time since deployment" (referred to as "time") on both, we controlled for the effects of time in the MRM models. The effects of time were modeled as a quadratic function, since the relation between time and war zone stress reactions has been shown to be curvilinear (38).

With respect to 5-HTTLPR genotype, we performed a series of preliminary analyses testing for allele load effects by comparing L'S' vs. S'S' genotypes. These analyses revealed no significant load effects (all p values >0.43). Thus we followed the recommendation of Hariri et al (39) and modeled genotype as a two-level variable (S' carriers vs. L' homozygotes). The predictors of war zone stress reactions in the MRM models included time (months since deployment), time^2, gender, war zone stressors (assessed monthly during deployment), 5-HTTLPR genotype (S' carrier vs. L'L'), and the interaction between 5-HTTLPR genotype and level of war zone stressor exposure.

Following Hedeker and Gibbons (40), we decomposed the monthly measure of war zone stressors into a between-

Table 1 Regression coefficients for each class of war zone stress reaction

	War zone stress reactions		
Predictor	**PTSD symptoms**	**Depressive symptoms**	**Anxiety symptoms**
Average level of stressors	.22***	.49*	1.12**
Change in level of stressors	.07	.62***	1.21***
5-HTTLPR genotype	−.18	−.14	−.23
Average stress x 5-HTTLPR genotype	.21*	.83*	1.36*
Change in stress x HTTLPR genotype	−.14	−.31	.20
Time (months since deployment)	.00	.03	−.06
$Time^2$	−.02***	−.04***	−.06***
Gender (male=0; female=1)	.50	2.86*	5.47*

PTSD – post-traumatic stress disorder, *p<0.05, **p<0.01, ***p≤0.001

soldier effect (the average level of stressors reported over the deployment period) and a within-soldier effect (the deviation from the "average level" of stressors for each soldier at each point in time, referred to as "change in war zone stressors"). Failing to decompose these effects would confound the between- and within-soldier effects, resulting in potentially misleading results (22).

All variables were centered at their grand mean so that results for every main effect would represent the average effect for the sample. Gender was included as a covariate in all the analyses, because of the observed linkage between gender and both depressive and anxiety symptoms.

RESULTS

Participants

The analyses were conducted on the data from 133 soldiers, who provided a total of 926 monthly assessments (mean number of assessments 6.96±5.62, median 5.0, range 1-18). The mean age of the final sample was 23.5±6.0 years. The large majority of the sample (85.7%) was male, and participants were predominantly Caucasian (72.9%), of which 24 (18% of the total sample) were Hispanic. Other ethnic/racial groups included African-Americans (9.8%), American Indians (12.8%), and Asian/Pacific Islanders (4.5%).

At pre-deployment, 20 (15.0%) participants met criteria for one or more current Axis I diagnoses, including substance use disorder (n=7, 5.3%), anxiety disorder (n=9, 6.8%), mood disorder (n=6, 4.5%), and adjustment disorder (n=5, 3.8%).

The mean duration of deployment was 393.0±67.8 days. The number of in-theater war zone stressors reported by a soldier in a given month ranged from 0 to 18 (mean±SD 2.01±2.40). The average level of stressors reported by each soldier over the course of deployment ranged from 0 to 14 (mean±SD 3.08±2.75). The month-to-month changes in war zone stressors for a soldier ranged from −9 to 9 (mean±SD 0.00±1.47).

Growth curve analyses of war zone stressors and war zone stress reactions over time

Initial MRM analyses were performed to examine the linear and quadratic effects of time for the three indices of war zone stress reactions. Results revealed that the quadratic trend over time was significant for all three measures: b=−.02, t (147)=−5.08, p<0.001 for PTSD symptoms; b=−.04, t (44)=−4.77, p<0.001 for depressive symptoms; and b=−.06, t (49)=−3.97, p<0.001 for anxiety symptoms. On the contrary, for all measures, the linear effect of time was not significant (p values >0.43). These results indicate that, subsequent to deployment, symptoms steadily increased, with a peak about 8 months after deployment, followed by a gradual return to initial levels around month 16.

The soldiers' exposure to war zone stressors over time followed a different pattern. Neither the linear nor quadratic trends were significant (p values >0.26), indicating that stressors remained relatively constant over the term of the soldiers' deployment.

Main effects of war zone stressors, 5-HTTLPR genotype and gender on war zone stress reactions

Results from the MRM analyses revealed that higher *average* levels of war zone stressors were significantly related to greater war zone stress reactions on all three measures: b=.22, t (137)=4.01, p<0.001 for PTSD symptoms; b=.49, t (135)=2.28, p<0.05 for depressive symptoms; and b=1.12, t (141)=3.22, p<0.01 for anxiety symptoms. Similarly, month-to-month *changes* in war zone stressors were positively related to concurrent levels of depressive symptoms (b=.62, t (60)=3.63, p=0.001) and anxiety symptoms (b=1.21, t (59)=4.14, p<0.001), but not PTSD symptoms (p>0.23). Females, in comparison to males, reported higher levels of both depressive symptoms (b=2.86, t (82)=2.12, p<0.05) and anxiety symptoms (b=5.47, t (92)=2.42, p<0.05). There was no significant main effect of 5-HTTLPR genotype on any of the three indices of war zone stress reactions (p values >0.55) (Table 1).

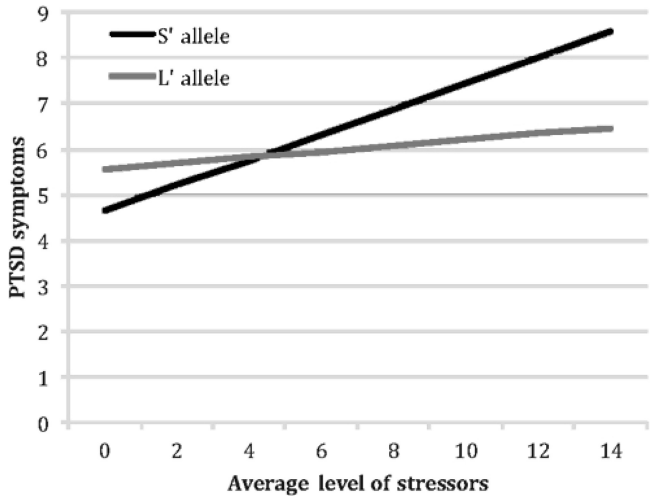

Figure 1 Moderating effects of 5-HTTLPR genotype on the emergence of post-traumatic stress disorder (PTSD) symptoms in response to increasing levels of war zone stressors

For war zone stressors, females tended to report slightly fewer stressors than males (b=−1.21, t (93)=1.93, p=0.057), perhaps reflecting different war zone assignments. There were no differences between the numbers of stressors experienced by S' allele carriers vs. L' homozygotes (p=0.97).

Effects of the interaction of war zone stressors by 5-HTTLPR genotype on war zone stress reactions

MRM analyses revealed significant interactions between 5-HTTLPR genotype and *average* level of war zone stressors during deployment for all three measures of war zone stress reactions: b=.21, t (121)=2.08, p<0.05 for PTSD symptoms; b=.83, t (126)=2.13, p<0.05 for depressive symptoms; and b=1.36, t (134)=2.12, p<0.05 for anxiety symptoms. However, none of the interactions between the 5-HTTLPR genotype and month-to-month *changes* in war zone stressors was significant (p values >0.28) (Table 1).

To examine the nature of these interactions between 5-HTTLPR genotype and average level of war zone stressors, we followed the recommendations formulated by Aiken and West (41). Using their approach, we calculated the relation between soldiers' average stress levels and their stress reactions separately for S' carriers and their L' homozygote counterparts (this approach uses the entire sample to calculate each simple slope, but computes these effects for each group of soldiers separately). For L' homozygotes, higher levels of average stress reported in the field did not predict higher symptoms: b=.07, t (85)=.86, p>0.39 for PTSD symptoms; b=−.12, t (108)=−.43, p>0.66 for depressive symptoms; and b=.11, t (116)=.24, p>0.81 for anxiety symptoms. In contrast, and consistent with our hypothesis, S' carriers responded to higher levels of average stress with higher levels of PTSD symptoms (b=.28, t (134)=4.01, p<0.0001); depressive symptoms (b=.71, t (138)=2.62, p=0.01), and anxiety symptoms (b=1.48, t (142)=3.39, p=0.001) (see Figures 1, 2 and 3).

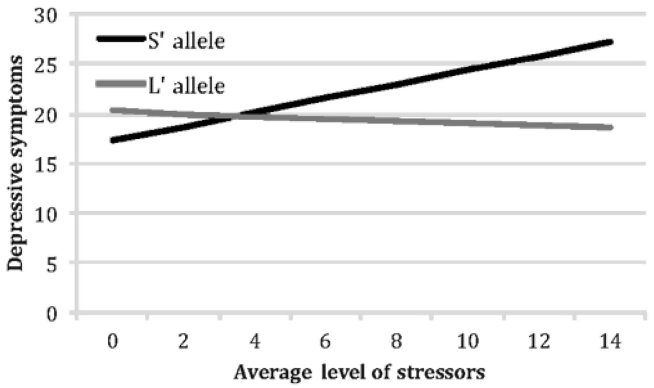

Figure 2 Moderating effects of 5-HTTLPR genotype on the emergence of symptoms of depression in response to increasing levels of war zone stressors

To investigate whether these findings were due to pre-existing psychopathology, we repeated these analyses controlling for lifetime history of an Axis I disorder (0 = no disorder, 1 = one or more Axis I disorders). Although a history of Axis I disorder was generally related to greater war zone stress reactions (b=.49, t (123)=1.85, p<0.07 for PTSD symptoms; b=2.48, t (103)=2.59, p=0.01 for depressive symptoms; and b=4.54, t (113)=2.89, p=0.005 for anxiety symptoms), all the significant effects reported above (including the interactions between genotype and level of stressors) were still significant after controlling for that history.

Effects of race in moderating the interactive effects

Because differences in the genetic backgrounds of individuals as represented by race can possibly confound the effects of specific genetic polymorphisms (42), MLM analyses were performed to examine the effects of race on the observed interaction effects of war zone stressors x 5-HTTLPR genotype for each of the three war zone stress reactions. Race was coded as white (n=97), African-American (n=13), and other (n=23), and was represented by two

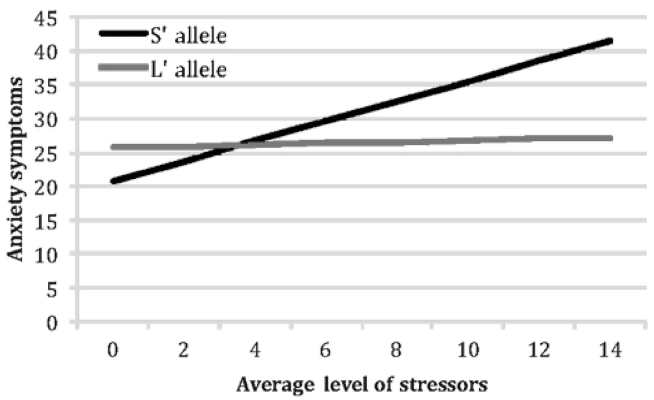

Figure 3 Moderating effects of 5-HTTLPR genotype on the emergence of symptoms of anxiety in response to increasing levels of war zone stressors

dummy variables. Interactions were formed between these two dummy variables and all of the terms predicting outcome in the MRM analyses.

The resulting analyses were consistent in showing no significant effects for race. Comparing models with and without race as a variable revealed no significant differences in their deviance scores (–2 log likelihoods): χ^2 (12)=6.18, p=0.91 for PTSD symptoms, χ^2 (12)=11.19, p=0.51 for depressive symptoms, and χ^2 (12)=10.88, p=0.54 for anxiety symptoms. These results indicate that race did not have a significant overall effect on any of the war zone reactions. Further, none of the race x war zone stressors x 5-HTTLPR genotype interactions for PTSD, depression or anxiety symptoms were significant (all p values ranged between 0.17 and 0.47), indicating that the observed war zone stressors x 5-HTTLPR genotype interactions were not influenced by soldiers' race.

DISCUSSION

Our in-theater web-based assessment allowed us to examine prospectively the main and interactive effects of 5-HTTLPR genotype and exposure to war zone stressors in predicting psychological dysfunction as they occur over the course of soldiers' deployment. The results provide novel evidence for an association between 5-HTTLPR genotype, level of exposure to war zone stressors, and symptoms of PTSD, depression and anxiety among soldiers deployed to a war zone. Our approach offers significant advantages over static, retrospective assessments used in previous combat stress risk studies (31).

The changes in war zone stress reactions over time were more complex than expected on the basis of previous reports of a positive association between length of deployment and war zone stress reactions (43,44). Each of the three targeted indices of war zone stress reactions – PTSD symptoms, depressive symptoms and anxiety symptoms – showed a significant inverted U-pattern in their respective growth curves over time. Stress reactions increased during the first eight months of deployment but then decreased to their earlier levels over the final eight months. This finding may reflect the effects of simple habituation or an increase in soldiers' sense of mastery in response to repeated confrontation with similar war zone stressors.

We found no evidence for a main effect of 5-HTTLPR genotype on any of the three war zone stress reactions. This finding is consistent with previous longitudinal studies showing that 5-HTTLPR moderates, but does not predict as a main effect, the impact of stress on risk for depression (45-48) and anxiety (28). Because it has been suggested that 5-HTTLPR genotype may influence one's risk of exposure to stressors via gene-environment correlation (49), we tested whether S' carriers were more likely to report heightened levels of exposure to war zone stressors relative to L' homozygotes. We found no such association between 5-HTTLPR genotype and war zone stressor severity. This finding is not surprising, since the potential threats (stressors) facing soldiers in a war zone are often not under the control of the individual soldier, whereas in non-military contexts, individual variables such as genetic factors and personality traits are more likely to influence the situations people face.

Consistent with previous studies (31,50), soldiers reporting more severe war zone stressors also reported higher levels of PTSD, depressive and anxiety symptoms. However, this main effect of war zone stressors was moderated by 5-HTTLPR genotype. Specifically, S' carriers responded to increasing levels of war zone stressors with increasingly greater war zone stress reactions across all three symptom domains. In contrast, there was no relationship between war zone stressors and the emergence of psychological symptoms for L' homozygotes. This finding is quite consistent with a diathesis-stress formulation of combat stress (51), and with 5-HTTLPR S' allele moderating risk for psychosocial dysfunction specifically in the wake of stressful life events (5).

Our observed GxE effect is likely mediated through the shaping of behavioral and neural responses to stress by the 5-HTTLPR. As described by Caspi et al (21), the 5-HTTLPR constitutes a genetic substrate for the personality trait of negative emotionality, which has been conceptualized as the propensity to experience aversive emotional states under conditions of stress (47,52,53). This expression of the S' allele on negative emotionality reflects the polymorphism's influence on serotonin signaling and, in turn, the development and functioning of a distributed cortico-limbic circuitry mediating behavioral and physiologic responses to stress, threat and trauma (14,15). Specifically, the S' (or S) allele of the 5-HTTLPR is associated with increased threat-related reactivity of the amygdala, which is critical for the expression of fear conditioning and anxiety (54).

Consistent with the greater attentional bias to threat observed in individuals with high negative emotionality and the importance of the amygdala in driving this bias, our group has recently shown, in a subset of these soldiers, that the S' allele is associated with pre-deployment attentional bias for aversive stimuli (55) as well as pre- to post-deployment shifts in gaze bias toward negative facial stimuli (56). We are now actively exploring the links between 5-HTTLPR genotype, threat-related amygdala reactivity, physiologic and behavioral indices of negative emotionality (38), and the emergence of war zone stress reactions.

Several design features of the study merit comment. First, we chose to employ a triallelic classification of the 5-HTTLPR accounting for rs25531 genotype. Among our sample, 3.4% of the L alleles were functionally reclassified as low expressing based on rs25531 status (i.e., L_G). These alleles would have been misclassified as high expressing alleles had we used the standard biallelic classification system. Although the different classification schemes did not affect the results of the current study, this misclassification issue may be one of the factors accounting for the dis-

crepancies in findings across studies. Second, our prospective design offers advantages over case only, case control and cross-sectional designs, by minimizing reporting biases associated with the retrospective assessment of exposure to the stressor. Third, our repeated assessment of war zone stressors and symptoms of PTSD, depression and anxiety allows us to examine patterns of change in symptoms as a result of repeated exposure to stressors. Converging evidence from research with rodents, primates and humans implicates repeated exposure to a stressor as a critical dimension in determining the emergence of psychopathology (21).

Several limitations of our study should also be noted. First, the sample size limits the power and stability of our findings across subgroups such as racial/ethnic minority participants. Second, although participants were recruited from ten different army units, we cannot rule out the possibility that our findings may not generalize to soldiers from outside Fort Hood. Replication with a larger sample across multiple army bases is warranted. Third, we chose to include only soldiers who had no history of prior deployment to a war zone, in order to eliminate the inferential ambiguity associated with prior exposure. However, this design decision precluded the investigation of 5-HTTLPR x prior deployment interaction effects. Fourth, while our evaluations of war zone stress reactions are based on validated self-report symptom measures, which offer the advantage of providing a convenient means for modeling change in psychological symptoms during deployment and for testing the main and interactive effects of genetic and environmental influences on those changes, they do not assess threshold diagnoses of PTSD, depression or other anxiety disorders. It should be noted that, upon their return from deployment, soldiers were administered several diagnostic interviews (i.e., the SCID and the Clinician-Administered PTSD Scale) by a trained clinician. Consistent with previous reports using stringent diagnostic criteria (4,57), only a small percentage (15%) met full criteria for a threshold mental disorder. The small numbers of threshold diagnoses precluded formal analyses of this outcome variable. However, the importance of assessing the full dimensionality of psychopathology, especially that of mood and anxiety, has emerged as a critical factor in advancing treatment and prevention (58). Thus, our focus on continuous measures of symptoms is likely an advantage in mapping the genetic and environmental substrates of risk for psychopathology.

Despite the emerging GxE literature on the importance of the 5-HTTLPR in moderating stress sensitivity and the surrounding debates (1,3,21,22), this is the first investigation to test the 5-HTTLPR x stress exposure interaction among soldiers deployed to a war zone. The current results serve to both replicate and extend the positive findings of previous studies in several important ways.

First, it has been suggested that both the type of stressor (specific vs. non-specific) as well as the method of stressor assessment (interview vs. self-report) may account for the discrepancy in findings across studies. Specifically, Caspi et al (21) assert that studies employing interview as opposed to self-report stressor assessments are more likely to show support for the 5-HTTLPR x stress interaction. Our study, which employed measures of war zone stressors via web-based self-reports, suggests otherwise. This difference may reflect the repeated nature of our self-report assessments, which may have led to more accurate reporting. Alternatively, it could be a result of the MRM analysis used in the current study, which increased power by including all subjects, regardless of missing data, and a large number of data points from repeated assessments.

Second, our findings point to the importance of stressor severity in moderating the impact of the 5-HTTLPR on soldiers' risk of experiencing psychological dysfunction while deployed. S' carriers showed equivalent levels of PTSD, depressive and anxiety symptoms relative to L' homozygotes when specific war zone stressors were low, but showed greater symptoms in all three dimensions as exposure to war zone stressors increased.

Thus, our data support a specific role for the 5-HTTLPR as a genetic vulnerability factor that potentiates the effects of war zone stress on the psychological well-being of deployed soldiers. More generally, they further the potential utility of this polymorphism, especially when combined with other genetic moderators of risk, to inform the development of biomarkers that predict relative resilience and vulnerability to stress broadly.

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RESEARCH REPORT

Comparative efficacy and acceptability of psychotherapies for depression in children and adolescents: a systematic review and network meta-analysis

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Previous meta-analyses of psychotherapies for child and adolescent depression were limited because of the small number of trials with direct comparisons between two treatments. A network meta-analysis, a novel approach that integrates direct and indirect evidence from randomized controlled studies, was undertaken to investigate the comparative efficacy and acceptability of psychotherapies for depression in children and adolescents. Systematic searches resulted in 52 studies (total N=3805) of nine psychotherapies and four control conditions. We assessed the efficacy at post-treatment and at follow-up, as well as the acceptability (all-cause discontinuation) of psychotherapies and control conditions. At post-treatment, only interpersonal therapy (IPT) and cognitive-behavioral therapy (CBT) were significantly more effective than most control conditions (standardized mean differences, SMDs ranged from −0.47 to −0.96). Also, IPT and CBT were more beneficial than play therapy. Only psychodynamic therapy and play therapy were not significantly superior to waitlist. At follow-up, IPT and CBT were significantly more effective than most control conditions (SMDs ranged from −0.26 to −1.05), although only IPT retained this superiority at both short-term and long-term follow-up. In addition, IPT and CBT were more beneficial than problem-solving therapy. Waitlist was significantly inferior to other control conditions. With regard to acceptability, IPT and problem-solving therapy had significantly fewer all-cause discontinuations than cognitive therapy and CBT (ORs ranged from 0.06 to 0.33). These data suggest that IPT and CBT should be considered as the best available psychotherapies for depression in children and adolescents. However, several alternative psychotherapies are understudied in this age group. Waitlist may inflate the effect of psychotherapies, so that psychological placebo or treatment-as-usual may be preferable as a control condition in psychotherapy trials.

Key words: Psychotherapies, depression, children, adolescents, cognitive-behavioral therapy, interpersonal therapy, psychodynamic therapy, problem-solving therapy, play therapy, waitlist, network meta-analysis

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Depression in young people has significant developmental implications, and accounts for the greatest burden of disease in this age group (1). The point prevalence of depression ranges from 1.9 to 3.4% among primary school children and from 3.2 to 8.9% among adolescents, and the incidence peaks around puberty (2-4). The average duration of a depressive episode in children and adolescents is about nine months, and 70% of patients whose depression remits will subsequently develop another depressive episode within five years, which suggests a substantial continuity between child and adolescent depression and depression in adulthood (3,4). Moreover, due to the atypical presentation and the high frequency of comorbidities (5,6), many cases of child and adolescent depression remain undetected, and do not receive the treatments they need (7-9). Thus, youths with depression experience serious impairment in social functioning, e.g. poor school achievement and relational problems with family members and peers (10), and show an elevated risk of self-harm and suicidal behaviors (11).

Clinical practice guidelines recommend that psychotherapy be considered as the first-line treatment for the management of mild to moderate depression in children and adolescents (12-15), and that medications be reserved for severe cases and those in which psychotherapy does not work (12,13). From the U.S., it is known that approximately three-quarters of the adolescents treated for depression have received some form of psychotherapy (16). Controversy regarding the efficacy and safety of antidepressant medications, along with the evidence of an increased risk of suicidal behavior in children and adolescents treated with some of these medications, has focused attention on the use of psychotherapy for this young population (17-21).

A number of psychotherapies are currently available for treating depression in children and adolescents (22,23). Although there is a broad consensus that various psychotherapies are beneficial for depression in youth patients, recent systematic reviews and meta-analyses have questioned this notion (24-28). The effect sizes of cognitive-behavioral

therapy (CBT) have recently decreased (24) compared to those documented in earlier meta-analyses (25). Some meta-analyses have reported that CBT is superior to other psychotherapies (26,27), whereas others have suggested that non-cognitive treatments (e.g., interpersonal therapy, IPT) work as well as cognitive ones (24,28). However, the conclusions of previous traditional meta-analyses were based on a limited number of trials with direct comparisons between two treatments, while some treatments have rarely or never been directly compared in a randomized controlled trial (RCT).

We implemented a network meta-analysis, a new methodological approach that allows the simultaneous comparison of multiple psychotherapeutic interventions within a single analysis, while preserving randomization (29). This approach was applied to integrate direct evidence (from studies directly comparing interventions) with indirect evidence (information about two treatments derived via a common comparator, e.g. waitlist) to estimate the comparative efficacy and acceptability of all treatments (30).

We previously investigated in this way the comparative efficacy of psychotherapies for adult depressed patients (31) and of augmentation agents in adult treatment-resistant depression (32). The aim of the current network meta-analysis was to provide a comprehensive and hierarchical evidence of the efficacy and acceptability of all psychotherapies in the treatment of depression in children and adolescents.

METHODS

Study protocol and search strategy

This systematic review is reported using PRISMA guidelines. The protocol has been registered with PROSPERO (CRD42014010014) and published in BMJ Open (33).

Eight electronic databases – PubMed, EMBASE, Cochrane, Web of Science, PsycINFO, CINAHL, LILACS, and ProQuest Dissertations – were searched from January 1, 1966 to July 1, 2014 with medical subject headings (MeSH) and text words. Also, ClinicalTrials.gov, the World Health Organization's trial portal and U.S. Food and Drug Administration (FDA) reports were reviewed. No language restrictions or restrictions on publication type were applied.

Additional studies were searched for in the reference lists of all identified publications, including relevant meta-analyses and systematic reviews. Relevant authors were contacted to supplement incomplete reports in the original papers or to provide new data of unpublished studies.

Study selection

Two independent researchers (BQ and YYL) selected studies for inclusion, with divergences resolved by consensus. They scanned citations at the title/abstract level and then retrieved a shortlist of potentially relevant studies in full text. These articles were reviewed in full to ensure that they satisfied all of the following criteria.

Only prospective RCTs, including cross-over and cluster-randomized trials, were selected. The study population had to consist of children or adolescents (aged from 6 to 18 years when initially enrolled in the primary study) who either had a diagnosis of major depression, minor depression, intermittent depression, or dysthymia based on standardized diagnostic interviews, or exceeded a predefined threshold for depressive symptoms using a validated depression severity measure.

Interventions included any manualized or structured psychotherapy, such as behavioral therapy, cognitive therapy, CBT, family therapy, IPT, play therapy, problem-solving therapy, psychodynamic therapy, and supportive therapy, regardless of duration and number of treatment sessions. RCTs comparing different modalities of the same type of psychotherapy (face-to-face, Internet or telephone), different treatment conditions (CBT or CBT plus sessions for parents) or different intervention formats (group or individual) were considered as the same node in the network analysis.

Comparators included another class of psychotherapy or a control condition, such as waitlist, no-treatment, treatment-as-usual, or psychological placebo.

To reduce inconsistency among trials, we excluded studies which recruited patients with treatment-resistant or psychotic depression; or involved combination therapies (i.e., combination of different psychological interventions, combination of psychotherapy with pharmacotherapy or another non-psychotherapeutic intervention); or focused on maintenance treatment or relapse prevention; or in which the psychotherapy intervention was not specifically aimed to treat depression. Studies were deemed eligible if they included patients with comorbid psychiatric disorders.

Outcome measures

The primary outcome was efficacy at post-treatment, as measured by mean change scores in depressive symptoms (self- or assessor-rated) from baseline to post-treatment. The secondary outcome was efficacy at follow-up, as measured by mean change scores in depressive symptoms from baseline to the end of follow-up. In addition, we extracted the data for short-term (1 to 6 months) and long-term (6 to 12 months) follow-up in each study. If a study reported data for more than one time within our pre-defined follow-up periods, we considered the last time point within the range. If participants received further treatments after the initial trial (e.g., continuous treatment or booster sessions), they were not included in the follow-up analysis.

Where depression symptoms were measured in a trial using more than one scale, we extracted data for the scale with the highest rank in a pre-defined hierarchy, based on psychometric properties and appropriateness for use with

children and adolescents and on consistency of use across trials (18). The Children's Depression Rating Scale (CDRS-R, 34) was adapted for children and adolescents from the Hamilton Depression Rating Scale (HAMD, 35), a tool validated and commonly used in adult populations. Both the CDRS-R and the HAMD have good reliability and validity (36) and had the highest rank in the hierarchy. The Beck Depression Inventory (BDI, 37) and the Children's Depression Inventory (CDI, 38) were the most commonly used among depression symptom severity self-rated scales and were ranked the second highest in the hierarchy.

The acceptability of treatment was operationally defined as all-cause discontinuation, as measured by the proportion of patients who discontinued treatment up to the post-intervention time point.

Data extraction and risk of bias assessment

Two independent researchers (BQ and YYL) classified psychotherapy approaches, extracted the data and assessed the risk of bias with good inter-rater agreement (kappa=0.86 to 0.90). The researchers independently extracted the key study parameters using a standardized data abstraction form and assessed the risk of bias in trials using the risk of bias tool from the Cochrane Handbook (39). Any disagreements were discussed with a third researcher (XYZ).

Data synthesis and analysis

We performed Bayesian network meta-analysis to compare the relative efficacy and acceptability of different psychotherapies and control conditions with each other from the median of the posterior distribution (29,30). The pooled estimates of standardized mean difference (SMD) with 95% credible intervals (CrIs) were calculated for continuous outcomes, and odds ratios (ORs) with 95% CrIs for categorical outcomes. The SMD is the difference in mean change scores from baseline to post-treatment between two groups divided by the pooled standard deviation (SD) of the measurements, with a negative SMD value indicating greater symptomatic relief (39). In the presence of minimally informative priors, CrIs can be interpreted similarly to confidence intervals, and at conventional levels of statistical significance a two-sided $p<0.05$ can be assumed if 95% CrIs do not include 0 (30).

A Cohen's effect size with Hedges' correction for small sample bias was calculated for all comparisons contained in the studies (40). If means and SDs were not provided, we calculated them from the p value or other statistical indices as described elsewhere (41). Results from intention-to-treat analysis (ITT) or modified ITT were preferred over results from completer analyses.

The pooled estimates were obtained using the Markov Chains Monte Carlo method. Two Markov chains were run simultaneously with different arbitrarily chosen initial values. To ensure convergence, trace plots and the Brooks-Gelman-Rubin statistic were assessed (42). Convergence was found to be adequate after running 50,000 samples for both chains. These samples were then discarded as "burn-in", and posterior summaries were based on 100,000 subsequent simulations. The node splitting method was used to calculate the inconsistency of the model, which separated evidence on a particular comparison into direct and indirect evidence (43). Probability values were summarized and reported as surface under the cumulative ranking curve (SUCRA) and rankograms, a simple transformation of the mean rank used to provide a hierarchy of the treatments and accounting for both the location and the variance of all relative treatment effects (44).

Network meta-analysis was performed using the WinBUGS software package (version 1.4.3, MRC Biostatistics Unit, Cambridge, UK) with random effects models for multi-arm trials. The other analyses were performed and presented by the Stata 11.0 and R 2.11.1 software packages.

We conducted subgroup analyses of data on primary outcome (efficacy in post-treatment) using the meta-regression model and calculating Somer's D (a correlation coefficient for a dichotomous and an ordinal variable) (45). We considered sex ratio (male-to-female ratio >1 vs. <1); age group (children aged 6-12 years vs. adolescents aged 13-18 years); number of sessions planned (≤ 8 vs. >8 sessions); intervention format (group vs. individual); method for defining the presence of depression (diagnosis of major depression, minor depression or dysthymia vs. severity of depressive symptoms); comorbid psychiatric disorders (with vs. without); risk of bias ("high risk" vs. "unclear risk" or "low risk"); sample size (≤ 50 vs. >50 patients); and year of publication (prior to 2000 vs. 2000 or following).

RESULTS

We analyzed 52 RCTs (46-97), including 116 conditions (psychotherapies and control conditions) and 3,805 patients (see the flow chart in Figure 1). Overall, 2,361 patients were randomized to nine psychotherapies (CBT, N=1149; IPT, N=344; supportive therapy, N=244; cognitive therapy, N=230; family therapy, N=134; play therapy, N=105; behavioral therapy, N=76; problem-solving therapy, N=44; or psychodynamic therapy, N=35). The remaining 1,444 patients were randomized to four control conditions (wait-list, N=419; no-treatment, N=284; treatment-as-usual, N=432; or psychological placebo, N=309).

The RCTs were published between 1980 and 2013. Sample sizes ranged from 9 to 399 patients per trial, with a median of 73. About three-fifths of total participants (59.9%) were females. Ten trials involved children only, 37 adolescents only, and five both. The mean age of participants was 14.7 years (range: 7-18 years). The mean number of sessions planned for psychotherapy was 11.4 (range: 5-36 sessions).

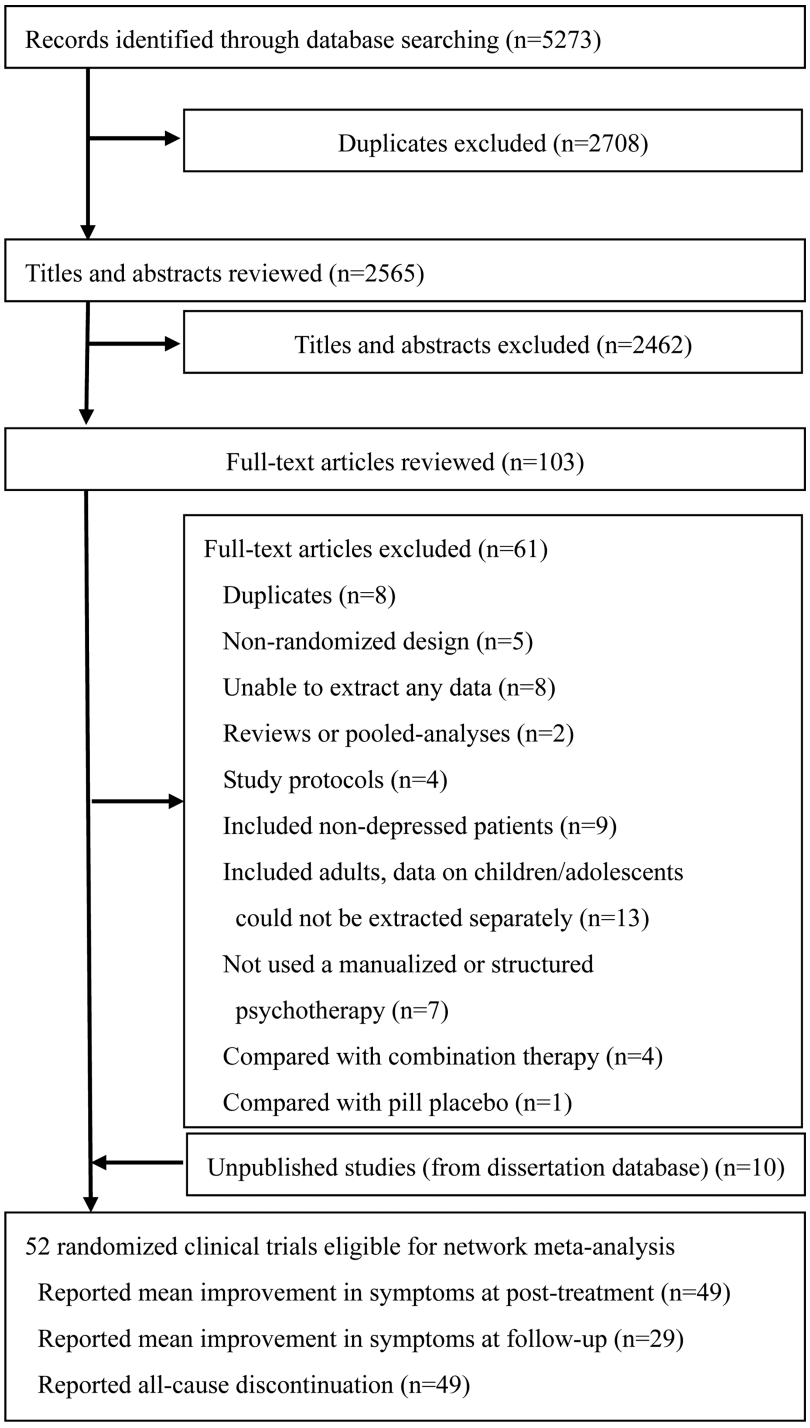

Figure 1 Flow chart of study selection

Further descriptive information about the included studies is given in Table 1.

Twenty-one studies (40%) investigated depressive disorders with standardized diagnostic assessments, while 27 (52%) explored depressive symptoms with a validated depression severity measure, and the remaining four used both methodologies. The median duration of acute phase treatment was 9.5 weeks (range: 4-36 weeks); that of follow-up period was 8.1 months (range: 1-24 months).

The risk of bias was rated as low concerning randomized generation of the allocation sequence in 25 RCTs, allocation concealment in six RCTs, masking of outcome assessors to treatment allocation in 20 RCTs, incomplete outcome data in 28 RCTs, and selective reporting in 46 RCTs.

Table 1 Characteristics of included studies

Trial	Definition of depression	Treatment conditions and sample size	Age (years, range)	Treatment duration (weeks)	Number of sessions	Follow-up duration (months)	Efficacy at post-treatment SMD (95% CI)	Efficacy at follow-up SMD (95% CI)
Ackerson et al, 1998 (46)	27-item CDI ≥10 and 21-item HAMD ≥10	CT=15 vs. WL=15	7-12	4	NA	NA	CT vs. WL: −2.05 (−3.12, −0.97)	NA
Asarnow et al, 2002 (47)	DSM-IV	CBT=11 vs. WL=12	4th to 6th grade	5	10	NA	NA	NA
Bolton et al, 2007 (48)	APAI ≥32	IPT=105 vs. PT=105 vs. WL=104	14-17	16	16	NA	IPT vs. WL: −0.53 (−0.81, −0.26); PT vs. WL: 0.19 (−0.08, 0.46)	NA
Brent et al, 1997 (49)	DSM-III-R	CBT=37 vs. FT=35 vs. SUP=35	13-18	12-16	NA	NA	CBT vs. SUP: −0.29 (−0.77, 0.19); FT vs. SUP: 0.25 (−0.25, 0.75)	NA
Butler et al, 1980 (50)	Self-report Depression Battery ≥59	CBT=14 vs. CT=14 vs. PBO=14 vs. NT=14	5th to 6th grade	10	10	NA	CBT vs. PBO: −1.12 (−1.94, −0.30); CBT vs. NT: −0.68 (−1.46, 0.10); CT vs. PBO: −0.77 (−1.56, 0.01); CT vs. NT: −0.17 (−0.92, 0.59)	NA
Clarke et al, 1995 (51)	CES-D ≥24	CT=76 vs. TAU=74	9th to 10th grade	5	15	12	CT vs. TAU: −0.21 (−0.57, 0.15)	CT vs. TAU: −0.13 (−0.51, 0.24)
Clarke et al, 1999 (52)	DSM-III-R	CBT=87 vs. WL=36	14-18	8	16	24	CBT vs. WL: −0.27 (−0.72, 0.18)	NA
Clarke et al, 2001 (53)	CES-D ≥24	CT=45 vs. TAU=49	13-18	8	15	24	CT vs. TAU: −0.33 (−0.75, 0.10)	CT vs. TAU: −0.13 (−0.5, 0.27)
Clarke et al, 2002 (54)	DSM-III-R	CBT=41 vs. TAU=47	13-18	8	16	24	CBT vs. TAU: −0.21 (−0.63, 0.21)	CBT vs. TAU: 0.08 (−0.34, 0.50)
Curtis, 1992 (55)	DSM-III-R	CBT=12 vs. WL=11	high school students	8	12	NA	CBT vs. WL: −1.57 (−2.63, −0.51)	NA
Dana, 1998 (56)	27-item CDI ≥12	CBT=10 vs. NT=9	8-13	4	8	1	CBT vs. NT: −0.07 (−0.97, 0.83)	CBT vs. NT: 0.01 (−0.89, 0.91)
De Cuyper et al, 2004 (57)	DSM-III-R	CBT=11 vs. WL=11	9-11	16	16	12	CBT vs. WL: 0.17 (−0.71, 1.05)	CBT vs. WL: −0.57 (−1.47, 0.33)
Diamond et al, 2002 (58)	DSM-III-R	FT=16 vs. WL=16	13-17	12	12	NA	FT vs. WL: −0.35 (−1.05, 0.35)	NA

Table 1 Characteristics of included studies *(continued)*

Trial	Definition of depression	Treatment conditions and sample size	Age (years, range)	Treatment duration (weeks)	Number of sessions	Follow-up duration (months)	Efficacy at post-treatment SMD (95% CI)	Efficacy at follow-up SMD (95% CI)
Diamond et al, 2010 (59)	21-item BDI ≥20	FT=35 vs. TAU=31	12-17	12	12	6	FT vs. TAU: −0.47 (−0.96, 0.02)	FT vs. TAU: −0.30 (−0.78, 0.19)
Eskin et al, 2008 (60)	DSM-IV	PST=12 vs. WL=11	15-18	6	6	12	PST vs. WL: −1.26 (−2.18, −0.35)	NA
Ettelson, 2003 (61)	DSM-IV	CBT=13 vs. WL=12	high school students	8	16	NA	CBT vs. WL: −1.00 (−1.84, −0.16)	NA
Fine et al, 1991 (62)	DSM-III-R	BT=30 vs. SUP=36	13-17	12	NA	9	BT vs. SUP: 0.46 (−0.13, 1.04)	BT vs. SUP: −0.18 (−0.81, 0.45)
Fischer, 1995 (63)	DSM-III-R	CBT=8 vs. PBO=8	12-17	5	5	NA	CBT vs. PBO: −0.47 (−1.47, 0.52)	NA
Fleming et al, 2012 (64)	CDRS-R ≥30	CBT=20 vs. WL=12	13-16	5	7	NA	CBT vs. WL: −1.41 (−2.21, −0.60)	NA
Hickman, 1994 (65)	DSM-III-R	BT=6 vs. TAU=3	8-11	10	10	1	BT vs. TAU: −0.57 (−2.00, 0.86)	BT vs. TAU: −0.68 (−2.13, 0.77)
Hoek et al, 2012 (66)	20-item CES-D ≥16	PST=22 vs. WL=23	12-21	5	5	2.5	PST vs. WL: −0.04 (−0.78, 0.70)	PST vs. WL: 0.04 (−0.73, 0.81)
Israel & Diamond, 2013 (67)	17-item HAMD ≥14	FT=11 vs. TAU=9	13-17	12	12	NA	FT vs. TAU: −1.26 (−2.25, −0.28)	NA
Jeong et al, 2005 (68)	SCL-90-R	PBO=20 vs. WL=20	middle school students	12	36	NA	PBO vs. WL: −0.87 (−1.52, −0.22)	NA
Kahn et al, 1990 (69)	27-item CDI ≥15	BT=17 vs. CBT=17 vs. WL=17	10-14	6-8	12	1	BT vs. WL: −1.03 (−1.75, −0.31); CBT vs. WL: −0.39 (−1.07, 0.29)	BT vs. WL: −0.61 (−1.30, 0.08) CBT vs. WL: −0.88 (−1.59,−0.18)
Kerfoot et al, 2004 (70)	MFQ ≥23	CBT=29 vs. TAU=23	13.7 (2.2), 14.1 (1.6)	8	8	NA	CBT vs. TAU: 0.11 (−0.47, 0.70)	NA
Lewinsohn et al, 1990 (71)	DSM-III	CBT=45 vs. WL=24	14-18	7	14	24	CBT vs. WL: −0.89 (−1.46, −0.32)	NA
Liddle & Spence, 1990 (72)	27-item CDI ≥19 and 17-item CDRS-R ≥ 40	CBT=11 vs. PBO=10 vs. NT=10	7-12	8	8	3	CBT vs. PBO: −0.57 (−1.45, 0.31); CBT vs. NT: −0.45 (−1.32, 0.42)	CBT vs. PBO: −0.25 (−1.11, 0.61) CBT vs. NT: −0.27 (−1.14, 0.59)
Listug-Lunde, 2004 (73)	27-item CDI ≥15	CBT=10 vs. WL=9	middle school students	7	13	3	CBT vs. WL: 0.09 (−0.86, 1.04)	CBT vs. WL: 0.27 (−0.69, 1.23)
Marcotte & Baron, 1993 (74)	21-item BDI ≥15	CBT=15 vs. WL=13	14-17	6	12	2	CBT vs. WL: −0.44 (−1.24, 0.36)	CBT vs. WL: −1.11 (−1.97, −0.26)
McCarty et al, 2013 (75)	MFQ ≥14	CBT=58 vs. SUP=62	11-15	12	12	NA	NA	CBT vs. SUP: −0.46 (−0.84,−0.08)

Table 1 Characteristics of included studies *(continued)*

Trial	Definition of depression	Treatment conditions and sample size	Age (years, range)	Treatment duration (weeks)	Number of sessions	Follow-up duration (months)	Efficacy at post-treatment SMD (95% CI)	Efficacy at follow-up SMD (95% CI)
Merry et al, 2012 (76)	CDRS-R ≥30	CBT=94 vs. TAU=93	12-19	4-7	7	3	CBT vs. TAU: −0.19 (−0.48, 0.09)	CBT vs. TAU: −0.13 (−0.42, 0.16)
Moldenhauer, 2004 (77)	27-item CDI ≥15	CBT=15 vs. PBO=11	12-17	6	6	1	CBT vs. PBO: −0.49 (−1.29, 0.30)	NA
Mufson et al, 1999 (78)	24-item HRSD ≥15	IPT=24 vs. PBO=24	12-18	12	12	NA	IPT vs. PBO: −0.72 (−1.31, −0.13)	NA
Mufson et al, 2004 (79)	24-item HAMD ≥10	IPT=34 vs. TAU=30	12-18	12-16	12	NA	IPT vs. TAU: −0.64 (−1.15, −0.13)	NA
Phillips, 2004 (80)	21-item BDI ≥10	CBT=33 vs. WL=31	15.5-20.5	6	6	NA	CBT vs. WL: −0.36 (−0.86, 0.13)	NA
Reed, 1994 (81)	DSM-III-R	BT=12 vs. PBO=6	14-19	12	6	2	NA	NA
Reivich, 1996 (82)	27-item CDI >10	CBT=27 vs. SUP=23 vs. NT=24	10-12	12	12	4	CBT vs. NT: −0.19 (−0.79, 0.42); SUP vs. NT: −0.24 (−0.85, 0.37)	CBT vs. NT: −0.45 (−1.04, 0.13); SUP vs. NT: 0.04 (−0.56, 0.65)
Reynolds & Coats, 1986 (83)	20-item BDI ≥12	BT=11 vs. CBT=9 vs. WL=10	Mean 15.65	5	10	5	BT vs. WL: −1.64 (−2.75, −0.53); CBT vs. WL: −1.93 (−3.20, −0.66)	BT vs. WL: −1.29 (−2.46, −0.13); CBT vs. WL: −1.91 (−3.21,−0.61)
Roberts et al, 2003 (84)	27-item CDI ≥15	CBT=25 vs. PBO=27	11-13	12	12	6	CBT vs. PBO: 0.08 (−0.49, 0.66)	CBT vs. PBO: −0.17 (−0.82, 0.47)
Rohde et al, 2004 (85)	DSM-IV	CBT=45 vs. PBO=48	13-17	8	16	12	CBT vs. PBO: −0.48 (−0.90, −0.06)	CBT vs. PBO: 0.20 (−0.22, 0.62)
Rossello & Bernal, 1999 (86)	DSM-III-R	CBT=25 vs. IPT=23 vs. WL=23	13-18	12	12	3	CBT vs. WL: −0.36 (−0.99, 0.28); IPT vs. WL: −0.88 (−1.56, −0.20)	NA
Rossello et al, 2008 (87)	DSM-III-R	CBT=52 vs. IPT=60	12-18	12	12	NA	CBT vs. IPT: −0.51 (−0.89, −0.14)	NA
Spence et al, 2003 (88)	21-item BDI ≥13	CBT=204 vs. NT=195	12-14	8	8	12	CBT vs. NT: −0.51 (−0.74, −0.28)	CBT vs. NT: −0.19 (−0.45, 0.08)
Stark et al, 1987 (89)	27-item CDI ≥16	CBT=9 vs. PST=10 vs. WL=9	9-12	5	12	2	CBT vs. WL: −1.71 (−2.83, −0.59); PST vs. WL: −0.88 (−1.83, 0.08)	NA
Stice et al, 2010 (90)	CES-D ≥20	CBT=89 vs. CT=80 vs. SUP=88 vs. PBO=84	14-19	6	6	24	CBT vs. PBO: −0.65 (−0.95, −0.34); CT vs. PBO: −0.07 (−0.37, 0.24); SUP vs. PBO: −0.26 (−0.56, 0.04)	CBT vs. PBO: −0.17 (−0.47, 0.13); CT vs. PBO: −0.05 (−0.36, 0.25); SUP vs. PBO: −0.32 (−0.62,−0.02)

Table 1 Characteristics of included studies *(continued)*

Trial	Definition of depression	Treatment conditions and sample size	Age (years, range)	Treatment duration (weeks)	Number of sessions	Follow-up duration (months)	Efficacy at post-treatment SMD (95% CI)	Efficacy at follow-up SMD (95% CI)
Tang et al, 2009 (91)	DSM-IV-TR	IPT=35 vs. TAU=38	12-18	6	12	NA	IPT vs. TAU: −1.00 (−1.48, −0.51)	NA
Trowell et al, 2007 (92)	DSM-IV, Kiddie-SADS	DYN=35 vs. FT=37	9-15	9	24.7/11	6	DYN vs. FT: 0.65 (0.18, 1.13)	DYN vs. FT: 0.21 (−0.26, 0.67)
Vostanis et al, 1996 (93)	DSM-III-R	CBT=31 vs. PBO=30	8-17	18	9	9	CBT vs. PBO: −0.38 (−0.91, 0.15)	CBT vs. PBO: −0.31 (−0.83, 0.22)
Weisz et al, 1997 (94)	26-item CDI ≥11	CBT=16 vs. NT=32	9.6	8	8	9	CBT vs. NT: −0.70 (−1.32, −0.08)	CBT vs. NT: −0.63 (−1.25, −0.02)
Wood et al, 1996 (95)	DSM-III-R	CBT=26 vs. PBO=27	9-17	Mean 9.2	Mean 6.4	6	CBT vs. PBO: −0.86 (−1.45, −0.26)	CBT vs. PBO: −0.11 (−0.71, 0.49)
Young et al, 2006 (96)	CES-D ≥16	IPT=27 vs. TAU=14	11-16	10-12	8	6	IPT vs. TAU: −1.04 (−1.72, −0.35)	IPT vs. TAU: −0.60 (−1.26, 0.06)
Young et al, 2010 (97)	CES-D ≥16	IPT=36 vs. TAU=21	13-17	10-12	8	18	IPT vs. TAU: −1.09 (−1.67, −0.51)	IPT vs. SUP: −0.90 (−1.55,−0.25)

APAI – Acholi Psychosocial Assessment Instrument depression symptom scale, BDI – Beck Depression Inventory, BT – behavioral therapy, CES-D – Center for Epidemiologic Study Depression Scale, CI – confidence interval, CDI – Children's Depression Inventory, CDRS-R – Children's Depression Rating Scale-Revised, CBT – cognitive-behavioral therapy, CT – cognitive therapy, FT – family therapy, HAMD – Hamilton Rating Scale for Depression, IPT – interpersonal therapy, MFQ – Mood and Feelings Depression Questionnaire, NT – no-treatment control, OR – odds ratio, PBO – psychological placebo, PT – play therapy, PST – problem-solving therapy, DYN – psychodynamic therapy, SADS – Schedule for Affective Disorders and Schizophrenia, SMD – standardized mean difference, SUP – supportive therapy, SCL-90-R – Symptom Check List-90-Revision, TAU – treatment as usual, WL – waitlist

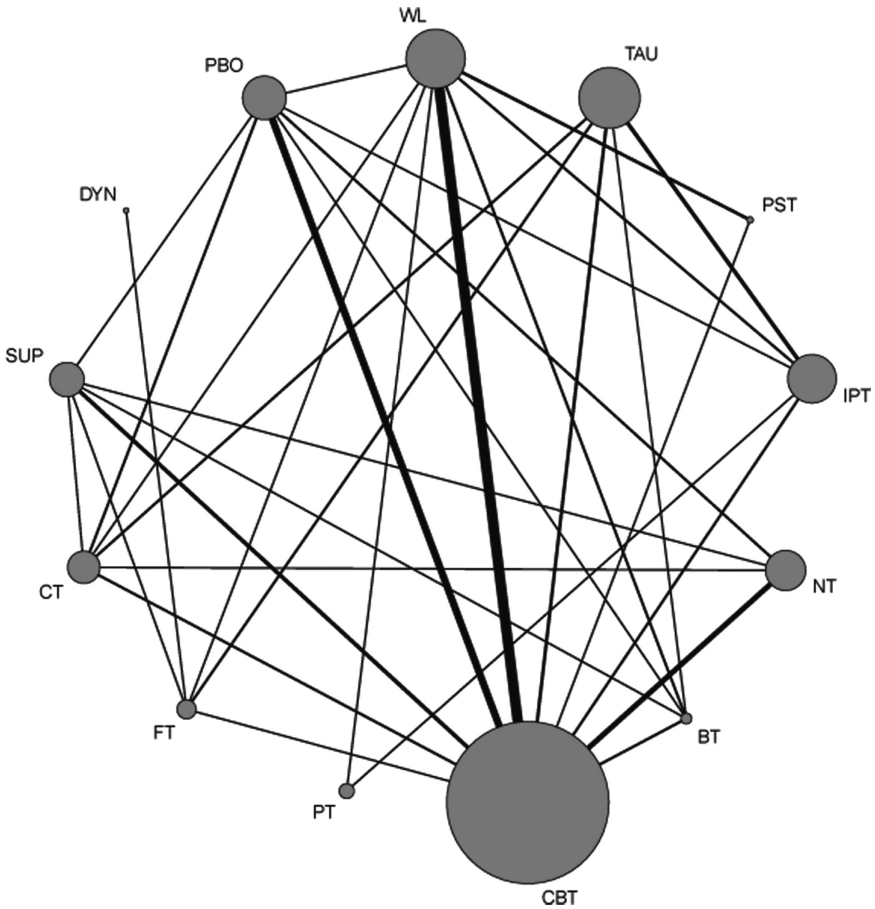

Figure 2 Network plot of evidence of all trials. The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every node is proportional to the number of randomized participants. BT – behavioral therapy, CBT – cognitive-behavioral therapy, CT – cognitive therapy, FT – family therapy, IPT – interpersonal therapy, NT – no-treatment control, PBO – psychological placebo, PT – play therapy, PST – problem-solving therapy, DYN – psychodynamic therapy, SUP – supportive therapy, TAU – treatment-as-usual, WL – waitlist

There were 13 nodes (nine psychotherapies plus four control conditions) and 33 comparisons in the network plot of evidence (Figure 2). Results of efficacy at post-treatment and follow-up assessments are shown in Figure 3. Concerning efficacy at post-treatment, only two psychotherapies (IPT and CBT) were significantly more effective than most control conditions, including psychological placebo, treatment-as-usual and waitlist (SMDs ranged from −0.47 to −0.96). IPT and CBT were also significantly more beneficial than play therapy (SMDs=−0.93 and −0.80, respectively). Among the nine investigated psychotherapies, only psychodynamic therapy and play therapy were not significantly more beneficial than waitlist. Waitlist was significantly inferior to no-treatment (SMD=−0.46).

Concerning efficacy at follow-up, IPT and CBT were significantly more effective than most control conditions, including treatment-as-usual, waitlist and, for CBT, no-treatment (SMDs ranged from −0.26 to −1.05). Also, IPT and CBT were significantly more beneficial than problem-solving therapy (SMDs=−1.10 and −0.90, respectively). Psychodynamic therapy and problem-solving therapy were not significantly more beneficial than waitlist. Waitlist was significantly inferior to all other control conditions, including placebo, treatment-as-usual, and no-treatment (SMDs ranged from −0.53 to −0.67).

Data about acceptability are shown in Figure 4. IPT and problem-solving therapy had significantly fewer all-cause discontinuations than CBT and cognitive therapy (ORs ranged from 0.06 to 0.33). Problem-solving therapy also had significantly fewer discontinuations than psychological placebo (OR=0.10; 95% CrI: 0.02 to 0.98).

Concerning efficacy at short-term follow-up, IPT was significantly more effective than problem-solving therapy and waitlist (SMDs=−0.99 and −0.95, respectively), and CBT was significantly more effective than cognitive therapy, problem-solving therapy, psychological placebo, and waitlist (SMDs ranged from −0.35 to −0.91). Behavioral therapy and supportive therapy were superior to waitlist (SMDs=−0.71, and −0.67, respectively). Waitlist was significantly inferior to psychological placebo (SMD=−0.52). In the analysis of efficacy at long-term follow-up, IPT was significantly more beneficial than CBT, cognitive therapy,

IPT	-0.20 (-0.67 to 0.31)	-0.44 (-0.97 to 0.11)	-0.47 (-0.98 to 0.06)	-0.22 (-0.95 to 0.51)	**-1.10 (-1.90 to -0.27)**	-0.33 (-0.95 to 0.31)	-0.46 (-1.01 to 0.10)	-0.38 (-0.91 to 0.17)	**-0.52 (-0.98 to -0.06)**	-0.43 (-1.35 to 0.49)	--	**-1.05 (-1.66 to -0.44)**
-0.13 (-0.49 to 0.23)	CBT	-0.24 (-0.51 to 0.00)	-0.27 (-0.56 to 0.00)	-0.02 (-0.67 to 0.59)	**-0.90 (-1.56 to -0.23)**	-0.14 (-0.54 to 0.27)	**-0.26 (-0.53 to -0.01)**	-0.19 (-0.41 to 0.04)	**-0.32 (-0.60 to -0.08)**	-0.23 (-1.08 to 0.59)	--	**-0.86 (-1.24 to -0.49)**
-0.19 (-0.72 to 0.34)	-0.07 (-0.49 to 0.36)	SUP	-0.03 (-0.36 to 0.31)	0.22 (-0.46 to 0.88)	-0.66 (-1.36 to 0.05)	0.11 (-0.32 to 0.55)	-0.02 (-0.36 to 0.32)	0.06 (-0.23 to 0.37)	-0.08 (-0.42 to 0.25)	0.01 (-0.86 to 0.86)	--	**-0.61 (-1.06 to -0.17)**
-0.27 (-0.75 to 0.23)	-0.14 (-0.54 to 0.27)	-0.08 (-0.60 to 0.46)	CT	0.25 (-0.40 to 0.87)	-0.63 (-1.34 to 0.09)	0.13 (-0.34 to 0.62)	0.01 (-0.37 to 0.38)	0.09 (-0.23 to 0.42)	-0.05 (-0.34 to 0.21)	0.04 (-0.81 to 0.87)	--	**-0.59 (-1.05 to -0.12)**
-0.29 (-0.85 to 0.28)	-0.16 (-0.66 to 0.35)	-0.09 (-0.69 to 0.50)	-0.02 (-0.62 to 0.58)	FT	-0.88 (-1.77 to 0.03)	-0.12 (-0.85 to 0.64)	-0.24 (-0.91 to 0.45)	-0.16 (-0.81 to 0.52)	-0.30 (-0.87 to 0.27)	-0.21 (-0.76 to 0.34)	--	**-0.84 (-1.55 to -0.10)**
-0.33 (-1.05 to 0.39)	-0.20 (-0.85 to 0.45)	-0.13 (-0.90 to 0.62)	-0.06 (-0.82 to 0.69)	-0.04 (-0.84 to 0.76)	PST	0.76 (-0.03 to 1.51)	0.64 (-0.07 to 1.35)	0.72 (0.01 to 1.41)	0.58 (-0.14 to 1.28)	0.67 (-0.42 to 1.72)	--	0.04 (-0.59 to 0.68)
-0.36 (-0.96 to 0.25)	-0.23 (-0.74 to 0.29)	-0.17 (-0.75 to 0.42)	-0.09 (-0.72 to 0.53)	-0.07 (-0.76 to 0.62)	-0.04 (-0.77 to 0.83)	BT	-0.13 (-0.61to 0.35)	-0.05 (-0.50 to 0.41)	-0.19 (-0.67 to 0.26)	-0.09 (-1.03 to 0.82)	--	**-0.72 (-1.21 to -0.23)**
-0.50 (-1.01 to 0.01)	-0.37 (-0.75 to 0.00)	-0.31 (-0.83 to 0.21)	-0.23 (-0.75 to 0.28)	-0.22 (-0.83 to 0.40)	-0.18 (-0.92 to 0.57)	-0.14 (-0.77 to 0.48)	NT	0.08 (-0.24 to 0.42)	-0.06 (-0.43 to 0.30)	0.03 (-0.86 to 0.89)	--	**-0.59 (-1.05 to -0.14)**
-0.60 (-1.03 to -0.18)	**-0.47 (-0.76 to -0.19)**	-0.41 (-0.89 to 0.07)	-0.33 (-0.79 to 0.11)	-0.31 (-0.88 to 0.24)	-0.28 (-0.97 to 0.43)	-0.24 (-0.82 to 0.33)	-0.10 (-0.54 to 0.34)	PBO	-0.14 (-0.48 to 0.17)	-0.05 (-0.92 to 0.80)	--	**-0.67 (-1.11 to -0.25)**
-0.68 (-1.04 to -0.32)	**-0.55 (-0.88 to -0.22)**	-0.49 (-1.00 to 0.01)	-0.41 (-0.84 to 0.00)	-0.39 (-0.91 to 0.10)	-0.35 (-1.07 to 0.36)	-0.32 (-0.91 to 0.26)	-0.18 (-0.67 to 0.30)	-0.08 (-0.49 to 0.33)	TAU	0.09 (-0.70 to 0.88)	--	**-0.53 (-0.97 to -0.08)**
-0.95 (-2.00 to 0.11)	-0.82 (-1.84 to 0.21)	-0.75 (-1.82 to 0.32)	-0.68 (-1.76 to 0.39)	-0.66 (-1.55 to 0.11)	-0.62 (-1.81 to 0.58)	-0.59 (-1.71 to 0.54)	-0.45 (-1.52 to 0.64)	-0.35 (-1.39 to 0.71)	-0.27 (-1.29 to 0.76)	DYN	--	-0.63 (-1.53 to 0.30)
-0.93 (-1.66 to -0.20)	**-0.80 (-1.55 to -0.06)**	-0.74 (-1.59 to 0.10)	-0.66 (-1.49 to 0.15)	-0.64 (-1.52 to 0.22)	-0.61 (-1.56 to 0.35)	-0.57 (-1.46 to 0.30)	-0.43 (-1.26 to 0.39)	-0.33 (-1.11 to 0.45)	-0.25 (-1.02 to 0.52)	0.02 (-1.23 to 1.26)	PT	--
-0.96 (-1.36 to -0.57)	**-0.83 (-1.09 to -0.58)**	**-0.77 (-1.25 to -0.30)**	**-0.69 (-1.15 to -0.25)**	**-0.67 (-1.20 to -0.15)**	**-0.63 (-1.25 to -0.02)**	**-0.60 (-1.12 to -0.09)**	**-0.46 (-0.91 to -0.02)**	-0.36 (-0.72 to 0.00)	-0.28 (-0.66 to 0.10)	-0.01 (-1.05 to 1.01)	-0.03 (-0.76 to 0.70)	WL

Treatment Efficacy at post-treatment (SMD with 95% CrI) Efficacy at follow-up (SMD with 95% CrI)

Figure 3 Relative effect sizes of efficacy at post-treatment and at follow-up according to network meta-analysis. Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For efficacy in post-treatment, standardized mean differences (SMDs) less than 0 favor the column-defining treatment. For efficacy in follow-up, SMDs lower than 0 favor the row-defining treatment. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values, and vice versa. Significant results are in bold and underlined. BT – behavioral therapy, CBT – cognitive-behavioral therapy, CT – cognitive therapy, FT – family therapy, IPT – interpersonal therapy, NT – no-treatment control, PBO – psychological placebo, PT – play therapy, PST – problem-solving therapy, DYN – psychodynamic therapy, SUP – supportive therapy, TAU – treatment-as-usual, WL – waitlist

PST											
0.29 (0.07 to 2.71)	IPT										
13.56 (0.02 to 48.71)	20.60 (0.07 to 84.43)	DYN									
0.19 (0.04 to 2.23)	0.90 (0.19 to 2.73)	0.03 (0.01 to 10.02)	SUP								
0.15 (0.03 to 2.45)	0.88 (0.13 to 3.12)	0.02 (0.01 to 11.94)	1.43 (0.14 to 5.97)	PT							
0.36 (0.03 to 1.40)	0.58 (0.17 to 1.42)	1.00 (0.01 to 6.27)	0.87 (0.19 to 2.51)	1.16 (0.13 to 4.41)	TAU						
0.31 (0.05 to 1.02)	0.57 (0.19 to 1.33)	1.07 (0.01 to 6.83)	0.85 (0.21 to 2.35)	1.07 (0.17 to 3.69)	1.15 (0.36 to 2.90)	WL					
0.10 (0.02 to 1.49)	0.30 (0.09 to 1.89)	0.02 (0.01 to 3.82)	0.42 (0.12 to 2.72)	0.37 (0.08 to 4.90)	0.66 (0.22 to3.03)	0.62 (0.19 to 3.48)	FT				
0.12 (0.03 to 0.88)	**0.33 (0.14 to 0.93)**	0.02 (0.00 to 4.74)	0.46 (0.18 to 1.45)	0.42 (0.11 to 2.85)	0.67 (0.30 to 1.84)	0.70 (0.37 to 1.44)	0.71 (0.23 to 3.52)	CBT			
0.27 (0.02 to 1.11)	0.45 (0.08 to 1.35)	0.79 (0.00 to 5.16)	0.63 (0.11 to 1.90)	0.86 (0.07 to 3.49)	0.54 (0.17 to 2.66)	0.56 (0.18 to 2.34)	1.22 (0.15 to 4.46)	1.08 (0.31 to 2.59)	NT		
0.10 (0.02 to 0.98)	0.31 (0.12 to 1.06)	0.02 (0.00 to 4.92)	0.41 (0.14 to 1.71)	0.38 (0.10 to 3.11)	0.60 (0.24 to 2.22)	0.63 (0.27 to 1.88)	0.64 (0.19 to 4.01)	0.89 (0.44 to 2.11)	0.83 (0.29 to 3.91)	AP	
0.08 (0.02 to 1.23)	0.24 (0.07 to 1.59)	0.01 (0.00 to 5.32)	0.37 (0.12 to 1.79)	0.30 (0.07 to 3.92)	0.49 (0.14 to 3.10)	0.51 (0.15 to 2.77)	0.53 (0.13 to 4.97)	0.71 (0.23 to 3.40)	0.67 (0.18 to 5.30)	1.24 (0.20 to 4.07)	BT
0.06 (0.01 to 0.60)	**0.16 (0.06 to 0.71)**	0.01 (0.00 to 2.88)	0.22 (0.07 to 1.11)	0.20 (0.05 to 1.97)	0.35 (0.14 to 1.18)	0.34 (0.13 to 1.24)	0.36 (0.10 to 2.36)	0.62 (0.19 to 1.58)	0.44 (0.14 to 2.63)	0.68 (0.17 to 1.88)	0.86 (0.12 to 3.15)

Treatment Acceptability outcome (OR with 95% Crl)

Figure 4 Relative effect sizes of acceptability from network meta-analysis. Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For acceptability, odds ratios (ORs) smaller than 1 favor the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underlined. BT – behavioral therapy, CBT – cognitive-behavioral therapy, CT – cognitive therapy, FT – family therapy, IPT – interpersonal therapy, NT – no-treatment control, PBO – psychological placebo, PT – play therapy, PST – problem-solving therapy, SUP – supportive therapy, TAU – treatment-as-usual, WL – waitlist

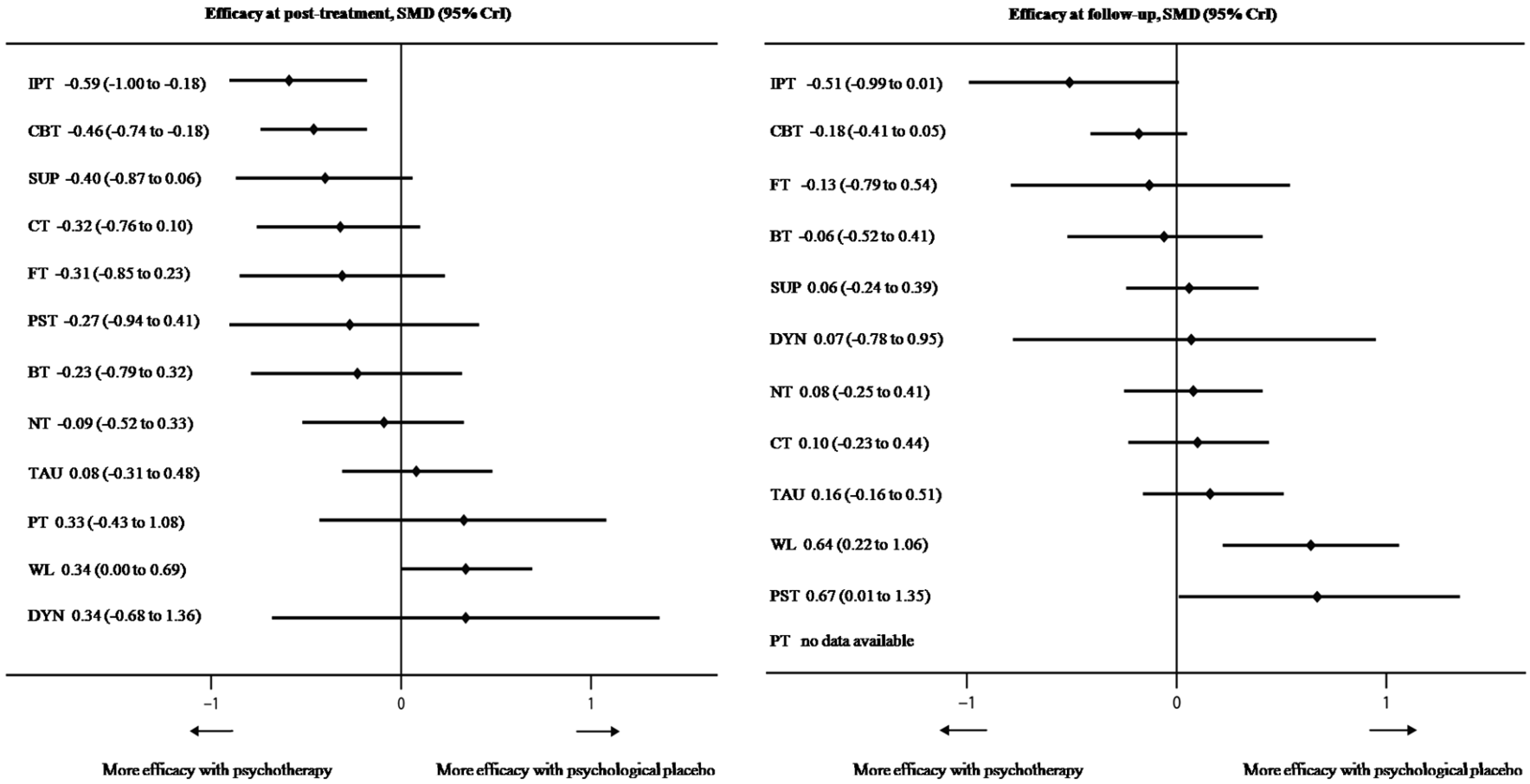

Figure 5 Forest plots of network meta-analysis results for efficacy with psychological placebo as reference. Standardized mean differences lower than 0 favor psychotherapy. BT – behavioral therapy, CBT – cognitive-behavioral therapy, CT – cognitive therapy, FT – family therapy, IPT – interpersonal therapy, PT – play therapy, PST – problem-solving therapy, DYN – psychodynamic therapy, SUP – supportive therapy, SMD – standardized mean difference, CrI – credibility interval

psychological placebo, treatment-as-usual, and no-treatment (SMDs ranged from −0.78 to −1.08), while CBT was not superior to any control condition.

There was no significant heterogeneity in the network meta-analysis concerning efficacy at post-treatment (SD =0.38; 95% CrI: 0.25 to 0.53), efficacy at follow-up (SD=0.12; 95% CrI: 0.01 to 0.31), and acceptability (SD=0.69; 95% CrI: 0.25 to 0.98), which suggests good interpretability of the results. There was very little evidence that direct and indirect effects were inconsistent (95% CrIs of differences between direct and indirect estimates included 0).

Forest plots of the network meta-analysis results for efficacy at post-treatment and at follow-up, with psychological placebo as reference, are shown in Figure 5. We also created hierarchies of effect size on the basis of SUCRA rankings for efficacy outcomes. The best treatment, according to the curves, was IPT at post-treatment (SUCRA=90.5%) and at follow-up (SUCRA=90.3%). The worst treatment, according to the curves, was waitlist at post-treatment (SUCRA=9.39%) and at follow-up (SUCRA=6.26%).

There was no evidence that the treatment effect was significantly modified by patients' clinical characteristics or risk of bias in the trials. However, IPT and CBT had less significant effects in studies in which patients were children, comorbid psychiatric disorders were present, and the year of publication was 2000 or following.

DISCUSSION

Our review of 52 RCTs suggests that, among the psychotherapies tested in children and adolescents with depression, only IPT and CBT are significantly more beneficial than most control conditions at post-treatment and at follow-up. Compared with other psychotherapeutic interventions, IPT and CBT were significantly more effective than play therapy at post-treatment, and more effective than problem-solving therapy at follow-up. Psychodynamic therapy and play therapy were not significantly more effective than waitlist in reducing depression symptoms at post-treatment and follow-up, although the limited number of trials available suggests the need for further research.

The acceptability of psychotherapies for depressed children and adolescents has seldom been investigated in previous meta-analyses. We found that IPT and problem-solving therapy had significantly fewer all-cause discontinuations than CBT and cognitive therapy. A possible interpretation is that a protocol putting emphasis on cognitive changes is more difficult for young people to engage in.

Our finding that waitlist was inferior to other control conditions (including no-treatment, treatment-as-usual and psychological placebo) seems to support the idea that waitlist may act as a "nocebo condition" in psychotherapy trials (98). In the case of child and adolescent depression, alternative hypotheses may be proposed to interpret this finding. First, placebo response in child and adolescent depression may be particularly high (17,99). Second, patients who are allocated to no-treatment may actively seek other treatments, while those on waitlist do not, as they are waiting for the intervention to be delivered (98). Anyway, the use of waitlist may inflate the treatment effect of psychotherapies in clinical trials, and the use of psychological placebo or treatment-as-usual is likely to provide a more robust comparison.

In our analysis, IPT and CBT demonstrated a robust effect over short-term follow-up, but only IPT had a beneficial effect over long-term follow-up. The theory behind IPT may particularly ring true for young people, as interpersonal difficulties may be more likely to drive psychopathology at this age (100). However, this finding was based on few trials, and requires further validation.

Subgroup analyses suggested no significant moderation of the treatment effect by different patient characteristics and intervention settings. Nonetheless, compared to psychological placebo, IPT and CBT showed less robust effects in studies on children with depression or on patients with comorbid disorders, and in more recently published trials. These findings are consistent with those from previous literature (26,101,102), but require further confirmation due to the relatively small size of the subgroups.

There were some limitations in the current study. Network meta-analysis assumes that some treatment arms are similar in rationale and procedure, allowing us to group them together as one node in the network (103). However, the classification of psychotherapeutic interventions for child and adolescent depression remains provisional. For instance, the treatments implemented in the trials we included under the heading "family therapy" were somewhat heterogeneous. Moreover, treatment-as-usual may be very different in various mental health care contexts, and it may be difficult to differentiate between no-treatment and treatment-as-usual in clinical practice, because when someone is assigned to no treatment, he/she can seek some form of usual care (98).

We excluded studies on treatment-resistant depression and psychotic depression, to reduce heterogeneity and inconsistency among trials. This may have led, however, to an overestimation of the effect size in the present meta-analysis, because the most difficult cases were not considered. Also, we could not include data on adverse effects, cost-effectiveness, quality of life outcomes and suicide, because they were lacking in almost all studies, although these variables are important for clinicians and patients to make decisions on selecting appropriate treatment.

In conclusion, our review supports the notion that IPT and CBT, when available, should be the initial choice of psychological treatment for depression in children and adolescents. However, several alternative treatment options are understudied in this age group, and further research on moderators of treatment effect are needed. Waitlist may inflate the treatment effect of psychotherapies, and psychological placebo or treatment-as-usual are likely to provide a more robust comparison in psychotherapy trials.

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Telemental health: a status update

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A rather large body of literature now exists on the use of telemental health services in the diagnosis and management of various psychiatric conditions. This review aims to provide an up-to-date assessment of telemental health, focusing on four main areas: computerized CBT (cCBT), Internet-based CBT (iCBT), virtual reality exposure therapy (VRET), and mobile therapy (mTherapy). Four scientific databases were searched and, where possible, larger, better-designed meta-analyses and controlled trials were highlighted. Taken together, published studies support an expanded role for telepsychiatry tools, with advantages that include increased care access, enhanced efficiency, reduced stigma associated with visiting mental health clinics, and the ability to bypass diagnosis-specific obstacles to treatment, such as when social anxiety prevents a patient from leaving the house. Of technology-mediated therapies, cCBT and iCBT possess the most efficacy evidence, with VRET and mTherapy representing promising but less researched options that have grown in parallel with virtual reality and mobile technology advances. Nonetheless, telepsychiatry remains challenging because of the need for specific computer skills, the difficulty in providing patients with a deep understanding or support, concerns about the "therapeutic alliance", privacy fears, and the well documented problem of patient attrition. Future studies should further test the efficacy, advantages and limitations of technology-enabled CBT, as well as explore the online delivery of other psychotherapeutic and psychopharmacological modalities.

Key words: Telemental health, telepsychiatry, Internet-mediated cognitive behavioral therapy, virtual reality exposure therapy, mobile therapy, mobile apps, short message service, depression, social phobia, specific phobias, post-traumatic stress disorder, obsessive-compulsive disorder

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The delivery of mental health services via telecommunication systems is having a remarkable expansion. For example, nearly 6% of all mobile health applications are now devoted to mental health (1).

Telemental health uses computer programs, Internet programs, teleconferencing, and smartphone applications for the remote delivery of mental health services, including diagnosis, assessment, symptom tracking, and treatment.

The aim of this paper is to review the current state of telemental health, focusing on its four main areas: computerized CBT (cCBT), Internet-mediated CBT (iCBT), virtual reality exposure therapy (VRET), and mobile therapy (mTherapy).

Articles were identified using PubMed, PsycINFO, ScienceDirect, and Wiley Online Library. The search was conducted using the terms "telepsychiatry", "telemental health", "computerized cognitive behavioral therapy", "assisted computerized psychotherapy", "unassisted computerized psychotherapy", "Internet therapy", "mobile cognitive behavioral therapy", "mobile therapy", "virtual reality exposure therapy", "virtual reality therapy", and "remote cognitive behavioral therapy". Google Scholar and Metacrawler search engines were also used to help identify unpublished material and book chapters.

The studies included in the review were limited to those published in English, with no restrictions placed on the country or year of publication. To the extent allowed by the literature, well-designed meta-analyses and larger, controlled trials with clearly defined outcome measures and inclusion and exclusion criteria were highlighted.

COMPUTERIZED AND INTERNET-MEDIATED CBT

Several forms of technology-enabled psychotherapy now exist. They differ in important ways with respect to the technology platform, level of clinician involvement, and type of therapy.

cCBT refers to the use of software programs to deliver standardized, automated psychotherapy via personal computers, CD-ROMs and desktop programs, or through interactive voice response (IVR) telephone systems. It dates back to the 1980s (2) and has been the first technology-enabled therapy delivery system to be formally studied.

Since conventional CBT is often a manualized, standardized treatment, it was thought to lend itself well to the use of technology in a way that minimized therapist involvement beyond the initial steps of program design (3). Thus, exploration of computer programs that would "conduct" CBT with patients began relatively early, before the Internet became a widespread phenomenon and the cornerstone of telemedicine and telemental health today (4).

Via specifically designed software programs, cCBT allows individuals to self-diagnose, personalize treatment goals, and employ standardized therapy tools to achieve symptom control and relapse prevention. It involves variable levels of therapist intervention: standalone or unassisted cCBT generally refers to the independent use of a standardized, software-based treatment program that almost completely bypasses the therapist (5), whereas guided or assisted cCBT typically incorporates minimal therapist involvement (6-8).

Beyond cCBT, the last decade has witnessed the remarkable growth of Internet-mediated psychotherapy. Several studies have explored the delivery of various psychotherapeutic approaches via the Internet, including interpersonal psychotherapy and online psychoeducation. However, most of the existing psychotherapy literature investigating the use of the Internet has focused on the delivery of CBT, an approach that has at times been called iCBT (e.g., 2,9).

Like cCBT, iCBT includes unassisted programs (5) as well as programs that incorporate minimal therapist involvement, usually via email or text message exchanges (assisted iCBT) (10). A third form of iCBT is "real-time" iCBT, which consists of live online conversations with "full" therapist involvement, and it may or may not include a video conferencing component (11,12).

Efficacy

Several meta-analyses have examined the efficacy of technology-enabled CBT. A meta-analysis of 14 randomized controlled trials (RCTs) and 2,976 subjects compared both assisted and unassisted cCBT to either waitlist or traditional CBT in the treatment of adult depression (13). cCBT showed a moderate post-treatment effect size on depressive symptoms when compared to the waitlist group, with equivalent outcomes compared to traditional CBT. However, traditional CBT performed better than cCBT in functional improvement and symptom reduction at the long-term follow-up points and was associated with lower dropout rates.

A large iCBT meta-analysis included 108 trials, of which 104 reported on clinical efficacy (N=9,410) and eight on cost-effectiveness (N=2,964) (2). Studies varied considerably in methodologies, outcome measures and conditions treated, and compared either unassisted iCBT to assisted iCBT or one of those interventions to a waitlist control or face-to-face therapy. Among the studies, 12 RCTs compared iCBT to traditional CBT in the treatment of depressive symptoms, social phobia, panic disorder, specific phobia (arachnophobia), sexual dysfunction and body dissatisfaction. Pooled results from the RCTs demonstrated similar efficacy on outcome measures as determined by effect size.

The literature on real-time iCBT with or without videoconferencing is more limited. In an RCT of adult subjects with major depressive disorder, 197 participants were assigned to ten sessions over 16 weeks of real-time iCBT with a live therapist and without videoconferencing, and 148 participants to an eight-month waitlist. Subjects in both groups continued to receive "usual care" by their general practitioners. At the four-month follow-up, 38% of subjects in the real-time iCBT vs. 24% in the control group responded, based on the Beck Depression Inventory (11).

Also, a study of 26 subjects (mean age: 30) with mood or anxiety disorders randomly assigned participants to either real-time iCBT with videoconferencing or traditional CBT. Participants received 12 weekly one-hour sessions and a follow-up session six weeks post-treatment. Real-time iCBT with videoconferencing was associated with a statistically significant reduction in symptoms of depression ($p<0.001$), anxiety ($p<0.001$) and "stress" ($p<0.001$), and had a similar efficacy to traditional CBT (3).

A more recent RCT investigated the efficacy of exposure and response prevention based CBT in the treatment of obsessive-compulsive disorder (OCD) in 30 subjects randomly assigned to 12 weeks of real-time iCBT with videoconferencing (N=10), self-help book-based exposure and response prevention (N=10), or a waitlist group (N=10). Post-treatment assessment demonstrated the superiority of real-time iCBT with videoconferencing: six participants (60%) receiving this treatment option achieved "clinically significant" improvement as assessed by the Yale-Brown Obsessive-Compulsive Scale; one participant (10%) demonstrated "reliable change" in response to self-help; and all participants in the waitlist group demonstrated "no change" (14).

Finally, group technology-enabled therapy has also received some research attention. A study compared the efficacy of real-time group iCBT with videoconferencing to face-to-face group CBT. It asked 18 subjects with depression or anxiety to select between the two interventions. Eight chose real-time iCBT with videoconferencing and appeared along the perimeter of the screen with the therapist in the center and could interact with one another and the therapist in real time; 10 chose traditional CBT. Subjects in both groups received 13 weekly one-hour group sessions. No significant difference was seen in efficacy, with approximately 60% in each group responding (15).

Special populations

Technology-enabled therapies have been studied for their potential use in special populations, including children and adolescents (16,17) and medically ill psychiatric patients (18).

A recent meta-analysis examined the efficacy of one unassisted iCBT program (BRAVE-ONLINE) and three assisted iCBT programs (BRAVE, COPE-A-LOT and "Think, Feel, Do") in the treatment of childhood anxiety disorders. Data from seven studies (five controlled trials, one case study and one cohort study) and 240 subjects aged 7 to 16 collectively demonstrated the efficacy of unassisted and assisted iCBT, with results comparable to those of traditional CBT (19).

Similarly, a study in 31 child and adolescent subjects with OCD (mean age: 11) randomly assigned participants to family real-time iCBT with a live therapist and videoconferencing or to a waitlist control. Participants received 14 family-based sessions and were assessed at one week and three months post-treatment. Subjects assigned to the waitlist group were assessed at four weeks post-randomization. Results demonstrated the superiority of real-time iCBT with videoconferencing: 81% response and 56% remission rates were seen among participants receiving iCBT, compared to 13% response and remission rates in the waitlist group (12).

Telemental health interventions in patients who have medical comorbidities have received some research attention as well. An RCT of 56 subjects with fibromyalgia and mild to moderate depression or anxiety randomly assigned participants to either six weeks of minimally assisted iCBT or continued unchanged pharmacological treatment. Subjects were assessed at one, six and 12 weeks post-intervention. At all assessment points, iCBT was associated with a significant

reduction in both the Fibromyalgia Impact Questionnaire scores and tender point sensitivity as assessed via physical examination (18).

Prevention

Several studies have explored the role of technology-enabled therapies in the prevention of psychiatric illness. One RCT tested the efficacy of unassisted iCBT in preventing depression in 163 university students who were randomly assigned to either five weeks of unassisted iCBT or a waitlist control. Subjects who received unassisted iCBT had significantly less depressive symptoms and improved literacy about depression at study end. The dropout rate, however, was significantly higher within the unassisted iCBT group compared to the control group (46.9 vs. 28.0%) (5).

In a relapse prevention study of iCBT in partially remitted depression, 303 subjects were randomly assigned to one of three interventions: unassisted iCBT, traditional therapy, or unassisted iCBT combined with traditional therapy (6). Individuals assigned to unassisted iCBT or unassisted iCBT combined with traditional therapy received nine online sessions. No statistically significant difference was seen in response and remission rates between unassisted iCBT and either traditional therapy or unassisted iCBT combined with traditional therapy. However, data at the 12-month follow-up demonstrated that traditional therapy was associated with a lower relapse rate compared to unassisted iCBT (20.7 vs. 31.3%).

Another study tested assisted iCBT in the prevention of relapse in partially remitted depression by randomly assigning 84 subjects to ten weeks of either 16 sessions of assisted iCBT or a waitlist control (7). Assessment at the 24-month follow-up demonstrated a significantly lower relapse rate in the assisted iCBT compared to the control group (13.7 vs. 60.9%).

Finally, a study examined the impact of minimally guided iCBT on the relapse of severe health anxiety (hypochondriasis) at six and 12 months after the conclusion of an RCT. Minimally guided iCBT yielded significantly better symptom control as well as increased cost-effectiveness compared to the waitlist control (20).

VIRTUAL REALITY EXPOSURE THERAPY

VRET refers to the use of virtual reality to conduct exposure therapy by mimicking real-life situations. The earliest experimental attempts on the use of virtual reality exposure as a treatment modality date back to 1992 (21), but it was only recently that the digital revolution brought about head-mounted displays, computer automated virtual environments, motion sensors and other sophisticated tools, making VRET environments more realistic, immersive and interactive. That, combined with the decreasing cost of the technology involved, has made VRET a potentially viable alternative to *in vivo* exposure therapy, and one that seems on the way to broader adoption (22).

VRET is generally conducted over six to 12 sessions, each lasting between 45 and 60 min (23). It has received less research attention than cCBT or iCBT, but efficacy data suggest its potential role in the treatment of several psychiatric conditions, including phobias, post-traumatic stress disorder (PTSD), OCD and substance use disorders.

Efficacy

Social anxiety disorder (social phobia)

Multiple studies provide evidence in support of VRET in the treatment of social anxiety disorder and public speaking anxiety. In a study of 41 subjects with social anxiety disorder, subjects participated in four sessions of cognitive restructuring, followed by four virtual sessions that targeted particular feared social settings (e.g., conference room, classroom, large auditorium). The study provided evidence that environments that better mimicked the feared scenario outperformed those that did not (24). A similar outcome was observed in a controlled trial that compared VRET to conventional CBT in the treatment of public speaking anxiety in a total of eight subjects. Participants were asked to deliver a speech before a real-life audience of five to nine individuals before and after completing four VRET sessions. All participants reported subjective improvement in public speaking anxiety immediately following, and several months after, the intervention (25).

Another study (N=88) compared the efficacy of 12 sessions of conventional CBT, 12 sessions of VRET, and a waitlist control in social anxiety disorder. VRET and conventional CBT proved equally superior to the waitlist group, with sustained improvement at one-year follow-up (26).

Specific phobias

Clinical trials of VRET in the treatment of specific phobias have also provided promising evidence. Several studies have explored the treatment of agoraphobia using VRET and have demonstrated superiority over a waitlist control (e.g., 27,28). A larger, more recent study assessed the efficacy of VRET in 80 subjects with long-standing (five years or more) agoraphobia. Subjects were randomly assigned to one of three groups: CBT with drug therapy ("CBT group"), N=30; CBT with drug therapy and VRET ("VRET group"), N=30; and drug therapy alone ("drug group"), N=20. Individuals in both the "CBT group" and the "VRET group" received five sessions of psychoeducation and cognitive restructuring, followed by six sessions of CBT or CBT and VRET. Both interventions were associated with clinical improvement, but VRET was associated with better adherence (29).

Claustrophobia has also received attention as a possible target for VRET. One study tested VRET in four subjects with claustrophobia, exposing them to eight virtual environments of increasing claustrophobic severity. Results demonstrated the efficacy of VRET both immediately after, and at the three-month follow-up (30). Another study in six subjects with claustrophobia suggested benefit from VRET, with the benefit shown to extend into real-life situations (31).

At least two controlled trials have demonstrated improved clinical outcomes for VRET vs. waitlist and equal benefit for VRET and conventional exposure therapy in the treatment of aviophobia (21,32,33). Finally, small studies have demonstrated improvement from VRET in the treatment of acrophobia (34,35).

Post-traumatic stress disorder

The first use of virtual reality in PTSD treatment involved a Vietnam War veteran (36), with a subsequent study in ten Vietnam War veterans demonstrating statistically significant reductions in both anxiety and avoidance levels that persisted at the three- and six-month follow-up points (37).

Other studies have suggested the efficacy of VRET in the treatment of PTSD resulting from non-war traumas. For example, a controlled study in subjects with PTSD stemming from the September 11, 2001 terrorist attacks compared VRET to a waitlist group. Of the 13 subjects who received VRET, five were resistant to previous treatments, and, of the ten receiving VRET who completed the study, nine experienced statistically significant improvement (38). Similarly, a study in ten subjects with PTSD resulting from abuse, crime assault or car accident randomly assigned participants to either conventional CBT or VRET. Both treatment modalities resulted in significant improvement in core PTSD symptoms (39). Finally, one article reviewed the possible role of VRET in the treatment of post-fall PTSD-like symptoms in elderly patients, providing evidence in favor of VRET and noting its ease of use in that patient population when compared to *in vivo* exposure (40).

Obsessive-compulsive disorder

Data on using VRET in the treatment of OCD are limited, in part because of the difficulty and cost of building programs that simulate the wide variability in OCD triggers among patients. However, a study comparing 30 subjects with OCD to 27 matched controls yielded an increased level of compulsive checking among subjects with OCD in response to virtual triggers compared to the control group, which suggested a role for VRET in OCD treatment and led to a subsequent, uncontrolled study in 24 subjects with arranging compulsions. Results from that study showed a decrease in OCD-related anxiety in response to VRET (41).

Substance use disorders

Treatment of drug dependence often involves strengthening the ability to resist using drugs when faced with triggers that provoke craving. Conventional CBT therapists usually rely on photographs and films to elicit craving, but have difficulty mimicking the behavior's typical setting. The need to better simulate real-life situations has led to the investigation of virtual reality as a more immersive environment in which to conduct therapy.

An early study investigating VRET in the treatment of five heroin-dependent subjects incorporated virtual cues that typically elicit craving. Both subjective (e.g., anxiety) and objective (e.g., autonomic activation) measures suggested the ability of virtual exposure to trigger real-life responses (42). More recently, a sample of 47 chronic smokers demonstrated hyperarousal when exposed to virtual smoking paraphernalia (43). To our knowledge, no study has compared VRET to conventional CBT in the treatment of substance use.

Other conditions

VRET has been preliminarily explored in the treatment of other conditions as well. For example, a study in 34 female subjects with eating disorders compared the efficacy of conventional CBT alone to CBT with VRET. Both groups demonstrated statistically significant improvement in body image, but participants receiving CBT with VRET showed greater improvement at the one-year follow-up point (44).

Further, and despite fear that virtual simulations might exacerbate symptoms in conditions already characterized by impaired reality testing, studies are beginning to assess VRET in psychotic individuals, with one schizophrenia trial (N=91) suggesting improved assertiveness and conversational abilities with VRET, as well as higher interest by subjects in virtual environment platforms than conventional treatment settings (45).

MOBILE THERAPY

mTherapy refers to the use of mobile phone devices, smartphones and mobile applications or "apps" in the delivery of mental health services. Its popularity has grown rapidly, as indicated by the title, "*Smartphone apps become surrogate therapists*", of a 2012 lay press article (46). Indeed, survey data suggest that mTherapy interventions may be favored over other telemental health tools by health care consumers (47).

Currently, over 3,000 mental health apps exist in Apple's App Store and Google's Google Play (48). They offer help with diagnosing (49), self-monitoring (1,48), symptom tracking and documentation (50), adherence to traditional therapy (51), and appointment and therapy homework reminders

(48). They can also provide convenient means for interacting with therapists between appointments (52). Although the literature on their efficacy remains scarce, some preliminary outcome data exist covering the more common forms of mTherapy.

Mobile apps

Mobile apps are the main form of mTherapy and include self-monitoring apps (52), apps that enhance self-awareness (53), apps that help with self-regulation (54), and CBT-inspired apps (mCBT) (55). A randomized trial of a self-monitoring app assigned 18 subjects to seven days of monitoring. The study demonstrated superiority over retrospective questioning about depression and stress (52). That was explained by decreased memory bias when gathering data and recording behaviors and thoughts as they occurred in real-life situations.

Another RCT in 118 depressed subjects aged 14 to 24 randomly assigned individuals to the use of mobile self-monitoring apps that tracked mood, stress level, and daily activities (N=68) or to a control group (N=46) where only daily activities were monitored. The use of mobile self-monitoring apps was associated with increased "emotional self-awareness", decreased depressive symptoms, rapid symptom improvement, and time savings compared to the control group (53).

Preliminary data from RCTs suggest benefit from mobile CBT as well. In one study, male subjects were assigned to one of two interventions: 11 received mobile CBT and 12 were assigned to waitlist. Individuals in the mobile CBT group received three group meetings conducted by a psychologist, in addition to self-reporting between meetings via a mobile CBT app that focused on clarifying personal values, goal setting, relaxation, mindfulness, and acceptance tools. It was hypothesized that between-meeting self-reporting would improve the continuity and impact of the face-to-face intervention. Indeed, mobile CBT was associated with a greater reduction in depressive symptoms than the control group at post-treatment, in addition to an improvement in reported overall health and working ability (55).

Another RCT in 35 subjects (mean age: 41 years) with major depressive disorder randomly assigned 15 to mobile CBT and 20 to cCBT. The "Get Happy" mobile app was used and consisted of six lessons to be completed over eight weeks. Both mobile CBT and cCBT were associated with a statistically significant reduction in depressive symptoms post-treatment and at the three-month follow-up (56).

A more recent study compared the efficacy of apps for mobile CBT and for mobile interpersonal therapy in treating social anxiety disorder. Fifty-two subjects were randomly assigned to receive either mobile CBT (N=27) or mobile interpersonal therapy (N=25). Mobile CBT performed better than mobile interpersonal therapy as measured by the Liebowitz Social Anxiety Scale, both post-treatment and at the three-month follow-up (between group Cohen's d=0.64) (57).

Text messaging or short message service

Text messaging, or short message service (SMS), has been used as an mTherapy intervention that allows for the immediate delivery of interventional messages and reminders of health goals, appointments and therapy homework (58). Preliminary studies have investigated it in the treatment of conditions such as major depression and psychotic disorders.

A study in 54 subjects with major depression and comorbid alcohol use disorder randomly assigned participants to either receiving twice-daily supportive text messages (N=26), or to a waitlist group where participants received "thank you" text messages once every 14 days (N=28). Subjects were followed for up to three months. Results, as assessed by the Beck Depression Inventory, showed a statistically significant difference in favor of text messaging when compared to the waitlist control (59).

Phone calls

Voice phone calls are an older form of mTherapy and have been used in the treatment of various psychiatric conditions, including anxiety disorders and depression. An RCT assessed phone-based psychotherapy in the reduction of suicidal ideation and self-harm by randomly assigning 68 subjects to either brief phone treatment alongside traditional face-to-face psychotherapy (N=34) or only face-to-face psychotherapy (N=34). Voice calls focused on mood assessment, provision of reassurance, problem-solving, and medication training. Assessment at six and 12 months following therapy initiation revealed that subjects also receiving phone psychotherapy had significantly less suicidal ideation and other depressive symptoms (60).

DISCUSSION

To a large degree, the potential advantages of telemental health mirror those of telemedicine and include improved access to care, especially for patients who live in areas that are under-served by mental health professionals, who have physical limitations that limit their ability to obtain traditional care, or whose work or other responsibilities prevent them from commuting to a regular clinic. In addition, the reduced need for office-related infrastructure may help contain costs and improve efficiency, helping make health care services more affordable overall. Advantages that are more specific to telemental health include reducing the stigma attached to visiting mental health facilities, as well as the ability to bypass diagnosis-specific obstacles to treatment (e.g., social anxiety-

or OCD-related fear of leaving the house or visiting a treatment setting).

Still, telemental health in its various manifestations remains somewhat controversial, in part because of ongoing concerns among patients and professionals about how technology platforms might impact the "therapeutic alliance" (61). Other problems include the lack of sufficient support, the inability to provide users with a deep understanding of their conditions, and the need for specific computer skills (62). Moreover, while CBT (and, by extension, exposure and response prevention) has been investigated to some degree, little data are available on other common forms of psychotherapy, and virtually no data exist on technology-assisted psychopharmacological care.

Of all technology-mediated therapies, cCBT and iCBT have been researched the most. Compared to cCBT, which was once limited to CD-ROMs and installable programs that required individuals to independently complete activities in the absence of therapist guidance, iCBT appears to be an advance in that it offers access to a broader variety of CBT programs, while also providing the opportunity for varying levels of therapist guidance. Research studies point to many successes for cCBT and iCBT across several psychiatric disorders and support a role for these interventions in modern psychotherapy delivery. Still, a major limitation of cCBT and, perhaps to a lesser degree, iCBT appears to be patient attrition (16).

VRET is a younger technology-enabled therapy that may possess advantages over traditional forms, especially when it comes to recreating challenging exposure situations, such as airplanes (for aviophobia) or bar settings (for alcohol-related disorder). Compared to traditional CBT, VRET may have the added advantage of additional control over the exposure exercise and a sense of increased safety when confronting phobic stimuli (63). This therapy, however, remains inadequately tested and not widely available, in part due to the need for infrastructure investment and training (64). With the increased availability and affordability of simulation technology, as evidenced by the current availability of highly sophisticated and immersive video games, VRET may become a more reasonable adjunct to, or possibly replacement for, conventional exposure therapy in certain disorders.

The most recent chapter in the digital revolution has been the dramatic rise of mobile technologies, including smartphones and associated apps. A parallel move has occurred within telemental health, where mental health apps have seen remarkable growth. Among other goals, they purport to help with self-monitoring and the very targeted delivery of therapeutic interventions. Compared to other forms of telemental health, a main advantage of mTherapy is its portability, which can make available data on behaviors, thoughts and coping strategies in real time, and help design highly specific, contextualized interventions. High attrition rates and respondent fatigue, however, seem to be serious limitations with mTherapy as well (52), and further evidence about efficacy is needed.

CONCLUSIONS

It has been estimated that up to 50% of all health care services will be conducted electronically by 2020 (65). Telemental health has been an integral part of the telemedicine movement and, given the "hands off" nature of many mental health services and the reduced need for treatment tools such as physical exams, lab tests and radioimaging, it may be poised to grow even faster than other medical fields.

So far, however, the rise of telemental health has generally outpaced scientific research, which limits the ability to make strong recommendations, especially when the substitution of online platforms for conventional care is being considered. Randomized clinical trials of adequate size and representation are clearly needed in order to establish the efficacy, safety and treatment adherence of available interventions, as well as to test some woefully understudied ones, such as Internet-enabled psychopharmacological care.

In addition, concerns about data and interaction confidentiality as well as compliance with health information regulations, such as the Health Insurance Portability and Accountability Act in the U.S., remain an obstacle to adoption by patients and providers alike and should be prioritized. Finally, insurer reimbursement needs to be assessed and advocated for in the case of interventions that have been shown to be effective and secure, especially if conventional alternatives are inaccessible, too expensive or insufficient on their own.

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Toward a new definition of mental health

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According to the World Health Organization (WHO), 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).

This definition, while representing a substantial progress with respect to moving away from the conceptualization of mental health as a state of absence of mental illness, raises several concerns and lends itself to potential misunderstandings when it identifies positive feelings and positive functioning as key factors for mental health.

In fact, regarding well-being as a key aspect of mental health is difficult to reconcile with the many challenging life situations in which well-being may even be unhealthy: most people would consider as mentally unhealthy an individual experiencing a state of well-being while killing several persons during a war action, and would regard as healthy a person feeling desperate after being fired from his/her job in a situation in which occupational opportunities are scarce.

People in good mental health are often sad, unwell, angry or unhappy, and this is part of a fully lived life for a human being. In spite of this, mental health has been often conceptualized as a purely positive affect, marked by feelings of happiness and sense of mastery over the environment (2-4).

Concepts used in several papers on mental health include both key aspects of the WHO definition, i.e. positive emotions and positive functioning. Keyes (5,6) identifies three components of mental health: emotional well-being, psychological well-being and social well-being. Emotional well-being includes happiness, interest in life, and satisfaction; psychological well-being includes liking most parts of one's own personality, being good at managing the responsibilities of daily life, having good relationships with others, and being satisfied with one's own life; social well-being refers to positive functioning and involves having something to contribute to society (social contribution), feeling part of a community (social integration), believing that society is becoming a better place for all people (social actualization), and that the way society works makes sense to them (social coherence).

However, such a perspective of mental health, influenced by hedonic and eudaimonic traditions, which champion positive emotions and excellence in functioning, respectively (7), risks excluding most adolescents, many of whom are somewhat shy, those who fight against perceived injustice and inequalities or are discouraged from doing so after years of useless efforts, as well as migrants and minorities experiencing rejection and discrimination.

The concept of positive functioning is also translated by several definitions and theories about mental health into the ability to work productively (1,8), and may lead to the wrong conclusion that an individual at an age or in a physical condition preventing her/him from working productively is not by definition in good mental health. Working productively and fruitfully is often not possible for contextual reasons (e.g., for migrants or for discriminated people), which may prevent people from contributing to their community.

Jahoda (9) subdivided mental health into three domains: self-realization, in that individuals are able to fully exploit their potential; sense of mastery over the environment; and sense of autonomy, i.e. ability to identify, confront, and solve problems. Murphy (10) argued that these ideas were laden with cultural values considered important by North Americans. However, even for a North American person, it is hard to imagine, for example, that a mentally healthy human being in the hands of terrorists, under the threat of beheading, can experience a sense of happiness and mastery over the environment.

The definition of mental health is clearly influenced by the culture that defines it. However, as also advocated by Vaillant (11), common sense should prevail and certain elements that have a universal importance for mental health might be identified. For example, in spite of cultural differences in eating habits, the acknowledgement of the importance of vitamins and the four basic food groups is universal.

TOWARD A NEW DEFINITION OF MENTAL HEALTH

Aware of the fact that differences across countries in values, cultures and social background may hinder the achievement of a general consensus on the concept of mental health, we aimed at elaborating an inclusive definition, avoiding as much as possible restrictive and culture-bound statements.

The concept that mental health is not merely the absence of mental illness (1,8) was unanimously endorsed, while the equivalence between mental health and well-being/functioning was not, and a definition leaving room for a variety of emotional states and for "imperfect functioning" was drafted.

The proposed definition is reported herewith:

Mental health is a dynamic state of internal equilibrium which enables individuals to use their abilities in harmony

with universal values of society. Basic cognitive and social skills; ability to recognize, express and modulate one's own emotions, as well as empathize with others; flexibility and ability to cope with adverse life events and function in social roles; and harmonious relationship between body and mind represent important components of mental health which contribute, to varying degrees, to the state of internal equilibrium.

The addition of a note explaining what is meant in the definition by the expression "universal values" is deemed necessary, in the light of the misleading use of this expression in certain political and social circumstances. The values we are referring to are: respect and care for oneself and other living beings; recognition of connectedness between people; respect for the environment; respect for one's own and others' freedom.

The concept of "*dynamic* state of internal equilibrium" is meant to reflect the fact that different life epochs require changes in the achieved equilibrium: adolescent crises, marriage, becoming a parent or retirement are good examples of life epochs requiring an active search for a new mental equilibrium. This concept also incorporates and acknowledges the reality that mentally healthy people may experience appropriate human emotions – including for example fear, anger, sadness and grief – whilst at the same time possessing sufficient resilience to timeously restore the dynamic state of internal equilibrium.

All components proposed in the definition represent important but not mandatory aspects of mental health; as a matter of fact, they may contribute to a varying degree to the state of equilibrium, so that fully developed functions may offset an impairment in another aspect of mental functioning. For instance, a very empathetic person, highly interested in mutual sharing, may compensate for a moderate degree of cognitive impairment, and still find a satisfactory equilibrium and pursue her/his life goals.

The main reasons underlying the choice of the components included in the definition are provided hereafter.

Basic cognitive and social skills are regarded as an important component of mental health in the light of their impact on all aspects of everyday life (12-15). Cognitive skills include the ability to pay attention, remember and organize information, solve problems, and make decisions; social skills involve the ability to use one's own repertoire of verbal/non-verbal abilities to communicate and interact with others. All these abilities are interdependent and allow people to function in their environment. Reference to the "basic" level of these abilities is meant to clarify that mild degrees of impairment are compatible with mental health, while moderate to severe degrees of impairment, especially if not balanced by other aspects, may require support by other members of the society and a number of social incentives, such as facilitated job opportunities, financial benefits or *ad hoc* training programs.

Emotional regulation, i.e. the ability to recognize, express and modulate one's own emotions, is also regarded as an important component of mental health (16). It has been proposed as a mediator of stress adjustment (17,18), and a link between inappropriate or ineffective emotional regulation and depression has been found in clinical and neuroimaging studies (19-22). A variety of modulated emotional response options, that can be flexibly employed, contribute to an individual's mental health, and alexithymia (i.e., an inability to identify and express one's own emotions) is a risk factor for mental and physical disorders (23,24).

Empathy, i.e., the ability to experience and understand what others feel without confusion between oneself and others, enables individuals to communicate and interact in effective ways and to predict actions, intentions, and feelings of others (25). The absence of empathy is not only a risk factor for violence and a feature of antisocial personality disorder, but also impairs social interactions at all levels.

Flexibility and ability to cope with adverse events are also deemed important to mental health maintenance. Flexibility refers to the ability to revise a course of action in the face of unpredicted difficulties or obstacles, change one's own ideas in the light of new evidence, and adapt to changes that different life epochs or contingent situations may require. Lack of flexibility may result in great distress for a person undergoing sudden and/or important life changes, and is an important aspect of several psychiatric disorders, such as obsessive personality or delusional disorder (26).

The basic ability to function in social roles and to participate in meaningful social interactions is an important aspect of mental health and particularly contributes to resilience against distress; however, social exclusion and stigmatization often impair social participation, so any definition of mental health alluding to this aspect has to avoid "blaming the victim" and to carefully analyze social patterns of stigmatization, discrimination and exclusion that impair participation (27).

The inclusion of a harmonious relationship between body and mind is based on the concept that mind, brain, organism and environment are heavily interconnected, and the overall experience of being in the world cannot be separated from the way in which one's body feels in its environment (28). Disturbances of this interaction may result in psychotic experiences, eating disorders, self-harm, body dysmorphic disorder or poor physical health.

CONCLUSIONS

The definition of mental health drafted in this paper is aimed to overcome perspectives based on ideal norms or hedonic and eudaimonic theoretical traditions, in favor of an inclusive approach, as free as possible of restrictive and culture-bound statements, and as close as possible to human life experience, which is sometimes joyful, and at other times sad or disgusting or frightening; sometimes satisfactory, and at other times challenging or unsatisfactory.

The proposed definition is also compatible with the recovery movement perspective, in which recovery after an illness

is seen as a process aimed to attain a fulfilled and valued life by building on the functions spared by the illness, in spite of the fact that other functions have been impaired (29).

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The alternative DSM-5 model for personality disorders

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Differences among personality types and styles have been observed for centuries. What accounts for these differences – what makes each person's personality unique – has been debated for a very long time as well. As far back as the days of Hippocrates, it was recognized that there must be correlations between behavior patterns and human biology, and personality types and styles such as melancholic, phlegmatic and sanguine were thought to correlate with differential levels of "body humors" such as bile, phlegm and blood. These principles have stood the test of time, but today we have moved from theory to science and we speak of levels of neurotransmitters such as dopamine, serotonin and norepinephrine that correlate with different personality types and styles. And we recognize that a given individual's personality emerges from at least two sources: temperament (the "hardwired" genetic component) and character (the shaping and molding effects of experience – either healthy or disruptive – during early development, particularly childhood attachment processes).

While great progress has been made, it remains challenging to reach a broad consensus on the best way to classify different personality types, and to differentiate the normal range and variety of personality types from what we call personality disorders. A central feature of this debate has been whether to use a dimensional or a categorical system. The Five-Factor Model has been studied extensively in factor-analytic trait psychology research and has been widely heralded as a valid dimensional system to capture main variations in personality styles (1). This model, however, was derived mostly from studies of normal populations and has not been easily applicable to patient populations.

The DSM adopted a categorical system more compatible with disease classification systems used in the world of medicine. In its third edition, published in 1980, diagnostic criteria were developed that defined a set of eleven personality disorders, and these were placed on the second "axis" (Axis II) of the multi-axial system introduced in that edition of the manual (2). Later editions of the DSM reduced the number of personality disorders to 10 and established a uniform polythetic format for the diagnostic criteria of each disorder, requiring a designated number of criteria to be present to make a given diagnosis (e.g., any 5 of 9 criteria are required for a diagnosis of borderline personality disorder). Personality disorders in DSM-IV are organized in what I refer to as a "dimensionally-flavored categorical system", reflected in the three "cluster" groupings: Cluster A ("odd-eccentric"), Cluster B ("dramatic-emotional"), and Cluster C ("anxious-fearful") (3).

The criteria-defined DSM categorical system has been widely utilized worldwide and has served as a stimulus to research. Nevertheless, a number of problems and shortcomings of this approach have been identified (4,5). For most personality disorders, the number of criteria, or threshold, required to make the diagnosis was arbitrary, yet the categorical approach conveys the impression that the disorder is either present or it is not, rather than that a symptom and trait pattern can vary along a gradient of severity. Furthermore, the polythetic nature of the criteria sets involves extensive heterogeneity within diagnoses. For example, there are 256 ways that five out of nine criteria for the diagnosis of borderline personality disorder can be configured (5), and two patients could receive this diagnosis but share only one criterion.

Work began on DSM-5 over a decade ago, and in an early monograph entitled "A research agenda for DSM-V" it was noted that "well-informed clinicians and researchers have suggested that variation in psychiatric symptomatology may be better represented by dimensions than by a set of categories, especially in the area of personality traits" (6, p. 12). Once convened, the Work Group for Personality and Personality Disorders was charged to review the literature and explore the possibility of developing a dimensional approach to classification of personality disorders.

An initial draft of a prototype model was developed and posted on the DSM-5 website in 2010, along with all proposed changes being considered for DSM-5. After extensive feedback from written responses, professional audiences, and the DSM-5 Task Force itself, it was decided that the prototype model would not be workable. A criteria-based "hybrid" model was then developed and posted in 2011, followed by a final posted version in 2012. This model was studied in the DSM-5 field trials. The new model for borderline personality disorder, for example, showed good test-retest reliability (7) and was judged to be preferable to the DSM-IV model by clinicians in routine clinical practice and at academic centers participating in the field trials. Data were obtained (and later published) from an independent group of practitioners showing similar results (8).

The new model for personality disorders was presented to the entire DSM-5 Task Force, consisting of the overall chair and co-chair of the DSM-5 effort, along with the chairs of all of the DSM-5 Work Groups, and it was strongly and unanimously approved. However, several scientific and clinical committees that the American Psychiatric Association (APA) had established to review all proposed changes in the diagnostic manual felt that there was not sufficient

evidence at the time to validate the proposed new personality disorder model and to establish its clinical utility. The APA Board of Trustees then voted to sustain the DSM-IV diagnostic system for personality disorders, virtually unchanged, in the main section of DSM-5 and to include the proposed new model as an "alternative DSM-5 model for personality disorders" in Section III of DSM-5, the section referred to as "Emerging measures and models" (9). Although this result was a disappointment to the Work Group, it is encouraging that the new model is included in DSM-5 as an "alternative model", thus "officially" allowing its use by those who are interested, and stimulating research on it (see 5,10,11).

In the alternative model, the essential criteria to define any personality disorder are: a) moderate or greater impairment in personality functioning, and b) the presence of pathological personality traits. A "level of functioning" scale is provided, and sensitivity and specificity data supported the designation of "moderate impairment" as the appropriate threshold to indicate the presence of a personality disorder (12). As defined in the alternative model, personality functioning consists of the degree to which there is an intact sense of self (involving a clear, coherent identity and effective self-directedness) and interpersonal functioning (reflecting a good capacity for empathy and for mature, mutually rewarding intimacy with others). Pathological personality traits are organized into five trait domains (negative affectivity, detachment, antagonism, disinhibition, and psychoticism), each of which is further explicated by a set of trait facets reflecting aspects of the domain itself. This trait system has been shown to correlate well with the Five Factor Model (13).

One task taken up by the Work Group was to review the literature and assess the strength of the published data supporting the construct validity of each DSM-IV personality disorder, similar to the process carried out in the development of DSM-IV itself, which led to the removal of passive-aggressive personality disorder from the diagnostic manual as a discrete disorder, reconceptualizing it as a trait found in many different Axis I and Axis II conditions. The result of these reviews was to reduce the number of designated personality disorders to six (antisocial, avoidant, borderline, narcissistic, obsessive-compulsive, and schizotypal), and to specify the nature of the moderate or greater impairment in personality functioning, as well as to itemize the pathological personality trait domains and trait facets that characterize each disorder.

In addition, a new diagnosis called Personality Disorder-Trait Specified was established, replacing Personality Disorder Not Otherwise Specified in DSM-IV. This diagnosis can now be utilized as more than just a "rule-out" diagnosis – it indicates that a patient does meet the general criteria for a personality disorder, does not qualify for any of the six designated personality disorders, and has a pathological trait profile that can be individually portrayed (which can capture paranoid, schizoid, histrionic, and dependent traits if present, in addition to any other applicable trait facets).

Overall, there has been growing interest in this alternative model. Clinical experience and further research can help evaluate its validity, reliability, and clinical utility, and whether or not additional changes might be considered in future revisions of the diagnostic manual. One interesting model is being proposed for the ICD-11, i.e., to utilize a single diagnostic term of Personality Disorder rated on four levels of personality dysfunction: "personality difficulty" (a "Z" code implying no formal disorder), mild, moderate, and severe personality disorder (14). This proposal is somewhat analogous to the Personality Disorder-Trait Specified diagnosis of DSM-5.

One critique of the alternative model, voiced by a number of leaders in the personality disorder field, argued that the new model is too complicated and that clinicians will not use it (15). However, as described above, clinicians reported favorably on its clinical utility and its use for treatment planning and communication to colleagues, patients, and families. Also, a fair test of complexity is to compare all of DSM-IV personality disorder diagnoses with all of those in the new model. In fact, the number of criteria required to cover all diagnoses in the new model has been reduced by 43% compared to DSM-IV. Either version can be used prototypically as is common in clinical practice, so that the most prominent diagnostic pattern, such as borderline personality disorder, will command the highest priority in treatment planning, with the option to explore additional pathological features as appropriate.

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The Psychodynamic Diagnostic Manual – 2nd edition (PDM-2)

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For decades many clinicians, especially psychodynamic and humanistic therapists, have resisted thinking about their patients in terms of categorical diagnoses. In the current era, they find themselves having to choose between reluctantly "accepting" the DSM diagnostic labels, "denying" them, or developing alternatives more consistent with the dimensional, inferential, contextual, biopsychosocial diagnostic formulations characteristic of psychoanalytic and humanistic approaches. The Psychodynamic Diagnostic Manual (PDM) (1) reflects an effort to articulate a psychodynamically oriented diagnosis that bridges the gap between clinical complexity and the need for empirical and methodological validity. It has been strongly influenced by a similar effort, the Shedler-Westen Assessment Procedure (SWAP-200) (2,3), on which it has drawn extensively. The second edition of the PDM (PDM-2) (4,5) will be published in 2016 by Guilford Press.

The first edition of the PDM, spearheaded by S. Greenspan with help from N. McWilliams and R. Wallerstein, represented the collaborative efforts of members from five sponsoring organizations: the American Psychoanalytic Association, the International Psychoanalytical Association, the Division of Psychoanalysis of the American Psychological Association, the American Academy of Psychoanalysis and Dynamic Psychiatry, and the National Membership Committee on Psychoanalysis in Clinical Social Work. The PDM-2 will be sponsored also by the International Association for Relational Psychoanalysis and Psychotherapy.

The PDM-1 had four major sections: Adult Mental Disorders; Child and Adolescent Mental Health Syndromes; Infant and Early Childhood Disorders; and Conceptual and Empirical Foundations for a Psychodynamically Based Classification System for Mental Health Disorders. Schematically, except when evaluating infants and pre-schoolers (assessed with a specific multiaxial system), clinicians were encouraged to assess the following in all patients: level of personality organization and prevalent personality styles or disorders (Axis P); level of overall mental functioning (Axis M); symptoms and syndromes and the patient's subjective experience of them (Axis S).

The PDM aimed to promote integration between nomothetic understanding and the idiographic knowledge that is useful for individual case formulation and the planning of patient-tailored treatment. In focusing on the full range of mental functioning, it aspired to complement DSM and ICD efforts to catalogue symptoms and syndromes. In the Pocket Guide to the DSM-5 Diagnostic Exam (6), Nussbaum notes: "ICD-10 is focused on public health, whereas the PDM focuses on the psychological health and distress of a particular person. Several psychoanalytical groups joined together to create PDM as a complement to the descriptive systems of DSM-5 and ICD-10. Like DSM-5, PDM includes dimensions that cut across diagnostic categories, along with a thorough account of personality patterns and disorders. PDM uses the DSM diagnostic categories but includes accounts of the internal experience of a person presenting for treatment" (6, pp. 243-244).

Addressing the discomfort many clinicians have with categorical diagnosis (7), the PDM provided an alternative framework that attempts to "characterize an individual's full range of functioning – the depth as well as the surface of emotional, cognitive and social patterns" (1, p. 1). The PDM explicitly describes itself as a "taxonomy of people" rather than a "taxonomy of diseases", as an effort to describe "what one is rather than what one has" (1, p. 17). According to Stepansky (8), the exposure of the first edition in the U.S. has been extensive.

In October 2013, the American Psychoanalytic Association noted: "There is a place in the field for classifying patients based on descriptions of symptoms, illness course, and other objective facts. However, as psychoanalysts, we know that each patient is unique. No two people with depression, bereavement, anxiety or any other mental illness or disorder will have the same potentials, needs for treatment or responses to efforts to help. Whether or not one finds great value in the descriptive diagnostic nomenclature exemplified by the DSM-5, psychoanalytic diagnostic assessment is an essential complementary assessment pathway which aims to provide an understanding of each person in depth as a unique and complex individual and should be part of a thorough assessment of every patient. Even for psychiatric disorders with a strong biological basis, psychological factors contribute to the onset, worsening, and expression of illness. Psychological factors also influence how every patient engages in treatment; the quality of the therapeutic alliance has been shown to be the strongest predictor of outcome for illness in all modalities." (www.apsa.org). It went on to recommend the PDM for this complementary assessment.

In the aftermath of the death of S. Greenspan shortly after the 2006 publication of PDM-1, and the retirement of R. Wallerstein (who died in 2014; the PDM-2 will be

dedicated to both Greenspan and Wallerstein), the new edition required leadership representing both continuity and change, which we have attempted to provide. Several specific Task Forces were organized, each under the leadership of two editors: Adults - P Axis (N. McWilliams and J. Shedler); Adults - M Axis (V. Lingiardi and R. Bornstein); Adults - S Axis (E. Mundo and J. O'Neil); Adolescents (M. Speranza and N. Midgley); Children (N. Malberg and L. Rosenberg); Infancy and Early Childhood (A.M. Speranza and L. Mayes); Elderly (F. Del Corno and D. Plotkin); Tools (S. Waldron, F. Gazzillo and R. Gordon); Case Illustrations and PDM-2 Profiles (F. Del Corno, V. Lingiardi and N. McWilliams). The second edition will thus retain the basic multiaxial structure, but will be characterized by several important changes, including those that follow.

The Adult Personality section will be integrated and revised according to theoretical, clinical and empirical indications, especially those derived from measures such as the SWAP-200 (2,3,9) and its new versions (10,11) and applications (12,13), and from the Psychodynamic Diagnostic Prototypes (14). The section on Levels of Personality Organization will, in light of research since 2006 that indicates the clinical utility of this concept, include a psychotic level of personality organization (15).

In the M Axis, the number of mental functions will be increased from nine to twelve: capacity for regulation, attention and learning; capacity for affective range, communication and understanding; capacity for mentalization and reflective functioning; capacity for differentiation and integration; capacity for relationships and intimacy; self-esteem regulation and quality of internal experience; impulse control and regulation; defensive functioning; adaptation, resiliency and strength; self-observing capacities (psychological mindedness); capacity to construct and use internal standards and ideals; meaning and purpose. An assessment procedure with a Likert-style scale will be associated with each mental function.

The S Axis will enhance its integration with the DSM-5 and the ICD-10. The new edition will give a more exhaustive explanation of the rationale for the description of "affective states", "cognitive patterns", "somatic states" and "relationship patterns", and cite related clinical and empirical studies. It will more thoroughly emphasize both the subjective experience of the patient and the likely countertransference of the clinician (16-19).

Because there are significant psychological differences between young children and teenagers, an Adolescent section (age 11-18) will be separated from the Child section (4-10). The Special Section on Infancy and Early Childhood (IEC) will include a discussion of developmental lines and homotypic/heterotypic continuities of early infancy, childhood, adolescent and adult psychopathology, as these have been investigated in both clinical and empirical literatures. The PDM will give better definitions of the quality of primary relationships (child and caregivers), emphasizing the evaluation of family systems and their characteristic relational patterns, including attention to attachment patterns and their possible relationship to psychopathology and normative development.

There will be a section on Mental Health Disorders of the Elderly, absent in the first edition.

The PDM-2 will contain two special sections on Clinician-Friendly Tools (both PDM-2-derived and derived from prior studies) that are intended to help practitioners attain a better understanding of the overall approach embodied in the manual (20,21).

Finally, the PDM-2 will omit the extensive last section on supporting empirical articles, and will instead integrate more systematic references to research, especially as empirical studies inform more operationalized descriptions of the different disorders.

In summary, the PDM aims to detect and describe patients' characteristic mental experiences, thereby increasing the capability of clinicians to relieve the psychological distress of the distinctly individual patients who seek their help. It attempts to restore the connection between deep understanding and treatment, without the requirements of other diagnostic systems that they be useful for demographic studies, billing, institutional record-keeping, syndromal research, and other ancillary uses of diagnostic labels.

Without a counterpoint to the current tendency to focus more and more narrowly on discrete disorder categories, the clinical relationship may be jeopardized and even damaged. Avoiding this hazard is the main reason why the authors of both editions of the PDM have offered this complementary classification system to the mental health community.

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The critical ingredients of assertive community treatment

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In their paradigm-shifting study, Stein and Test (1) developed and evaluated a community mental health treatment model for people with serious mental illness that became known as assertive community treatment (ACT). Their approach challenged many standard practices and beliefs in psychiatry. Based on earlier work, they had concluded (2) that hospital training programs to prepare patients for community living after discharge were ineffective, and that providing training and support within community settings after discharge was far superior. The principle of *in vivo assessment, training and support* became a cornerstone of the ACT model. With the locus of contact in the community, ACT used *assertive outreach* to engage clients who were reluctant to keep appointments at a clinic.

Another critical ingredient of the ACT model was a *holistic approach* to services, helping with illness management, medication management, housing, finances, and anything else critical to an individual's community adjustment. ACT services included assistance in routine practical problems in living, such as shopping and using public transportation. Along with the focus on the client's immediate needs and personal goals, the shift in service delivery to community settings dramatically increased client engagement in and satisfaction with mental health services (3).

Drawing on their experience on hospital treatment teams, Stein and Test formulated the ACT model as requiring a *multidisciplinary team* of mental health professionals, providing intensive, timely, and personalized services, facilitated through frequent team meetings to review treatment plans and services. ACT was also conceived as a *direct service model,* with clinicians providing most needed services themselves rather than referring to other providers. Another feature of the model with far-reaching influence was *integration of services,* which has demonstrated advantages over brokered approaches (i.e., referring clients to other programs for many services). ACT teams integrated mental health treatment, housing, rehabilitation, and many other services, and tailored them to the needs and goals of each client.

Another core feature of the ACT model was a *low client-staff ratio* of approximately 10 clients per full-time ACT practitioner. This staffing pattern permitted multiple contacts each week with clients needing intensive support. In addition, teams provided *continuous coverage,* responding quickly to client emergencies, 24 hours per day, seven days per week. Finally, ACT teams committed to *long-term and continuous care*. Initially, the model promised lifelong care.

RESEARCH ON EFFECTIVENESS

In the decades following the Stein and Test (1) study, dozens of randomized controlled trials of ACT evaluated its effectiveness for promoting community reintegration of people with severe mental illness. Several reviews concluded that ACT was more effective than standard services in reducing hospital use and increasing community tenure (3), and numerous practice guidelines endorsed ACT as an evidence-based practice for the treatment of schizophrenia (4). The impact of ACT on outcomes other than hospital use and community tenure was less clear, though some studies found improvements in stable housing, symptom management, and quality of life (3).

Research also began to identify the client populations for which ACT was most effective. ACT was strongly effective and cost-effective for clients who returned repeatedly to psychiatric hospitals; conversely, it was less effective and clearly not cost-effective for infrequently hospitalized clients (5). Extensions of the ACT model to homeless people with severe mental illness aimed at reducing homelessness were also generally effective, especially when integrated with evidence-based housing models (6).

MODIFICATIONS

Although some proponents of ACT insisted on orthodoxy, most endorsed ACT as a flexible service model that could be augmented with other evidence-based practices to address specific target populations and outcome domains. Over time, many ACT teams incorporated substance abuse treatments, supported employment, and family psychoeducation (7). In addition, modified ACT teams tailored services for clients experiencing early episodes of psychosis (8), those with borderline personality disorder (9), and those with criminal justice histories (10). Recent attention has focused on enhancing the experience of recovery, especially functional recovery and quality of life (11). Most of these augmentations have not yet been carefully studied, and in some areas the results have been mixed, but overall these innovations represent significant progress in defining the ACT model.

ACT FIDELITY

Several research groups have operationally defined the critical ingredients of ACT by developing fidelity scales. These scales measure implementation of the essential features of a model and enable program leaders to achieve and maintain model standards. One widely-used scale, the Dartmouth ACT Fidelity Scale (DACTS) (12), has been a valid tool for determining whether programs follow ACT principles. A more recent scale expanded the DACTS to include greater specification of staff roles and assessment of recovery-oriented services (11).

A meta-analysis evaluating the relationship between ACT fidelity and reduction of hospital use employed two broad indices measuring critical ingredients of the ACT model: *staffing* (low client-staff ratio, optimal team size, and inclusion of psychiatrist and nurse in the team) and *organization* (e.g., ACT team provides care directly rather than brokering, daily team meeting, and 24-hour access) (13). Organization predicted significant reductions in hospital use, while staffing did not. Thus, this study provided empirical support for the organizational components of ACT, but cast doubt on the necessity of multidisciplinary staffing standards.

ABSORPTION IN STANDARD SERVICES

The widespread endorsement of ACT by mental health leaders encouraged many states in the U.S. as well as other countries to adopt it as a service model. However, several large-scale evaluations in the U.K. failed to show any advantage for ACT over standard services, leading one researcher to conclude that ACT was effective only in communities with inadequate community mental health systems and an overutilization of psychiatric hospitals (14), precisely because standard mental health services in the U.K. had already adopted many of the innovations pioneered by ACT. Similarly, controlled trials in the U.S., particularly in good service areas, have not consistently found better outcomes for ACT in recent years, as the U.S. has continued to sharply reduce the rate of hospitalization admissions and length of hospital stays. Internationally, ACT continues to be an attractive service model option in some nations, such as Japan (15), with poorly developed community mental health services and routine use of long-term hospitalizations.

CURRENT VIEWS OF THE CRITICAL INGREDIENTS OF ACT

Current mental health services researchers believe that the organizational features of ACT are sound, as proven by their widespread emulation, and that any complex intervention needs to be flexible over time to respond to changes in values, context, culture, and research. Although ACT may have lost its preeminence as the most empirically supported of all community mental health treatment approaches (14), its monumental contribution in providing a clear, operationally defined treatment model with extensive research support remains exemplary. Many critical ingredients of ACT have been assimilated into standard practice in progressive mental health systems.

Several core components of the original ACT model have not endured. The principle of time-unlimited support – i.e., that clients should receive ACT indefinitely – is not evidence-based, recovery-oriented, practical, or cost-effective, and it has essentially been dropped and replaced with policies encouraging graduation (16). The multidisciplinary concept has gradually transformed to recognize that team members need to learn new competencies continuously as evidence-based practices emerge.

Other limits of ACT have been acknowledged. ACT is not well suited to rural settings, because sparsely-populated communities lack a critical mass of service users requiring intensive mental health services. To accommodate rural settings, a Dutch hybrid service model called flexible ACT (FACT) has embedded a short-term ACT team within a clinical treatment team, providing intensive services for clients who are in crisis, with easy transition to and from usual services (17). Other modified versions of ACT to support transitions and flexibility have been developed (e.g., 18), but no clearly superior model has emerged.

Influenced by research on related care management models, specifications for the critical ingredients of the ACT model continue to expand. ACT teams now incorporate ingredients such as *a focus on recovery, shared decision making, outcome-based supervision, strengths-based treatment planning,* and *use of generic community resources* (7).

CONCLUSIONS

ACT was the leading model of community mental health services developed during the latter half of the 20th century. It facilitated deinstitutionalization and enabled successful community reintegration for thousands of people with serious mental illness. The key principles of ACT – outreach, delivery of services in the community, holistic and integrated services, and continuity of care – continue to influence the structure of mental health services in profound ways over much of the world.

The structure and flexibility of ACT has permitted myriad adaptations. Thus, ACT remains relevant for service systems and clients with multiple needs in many settings. Complex service models such as ACT must continue to adapt over time, as new concepts, new environments, new stresses, and new empirically-supported practices emerge.

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Need for a realistic appraisal of benzodiazepines

Some recent articles on benzodiazepine use (1,2) have been followed by one more wave of negative publicity about these medications, sometimes calling for more regulations of their prescribing (3) Is this criticism deserved and what is its basis?

The recent article by Olfson et al (1) does not really provide any new information about benzodiazepines. It simply informs us about the approximate percentage of U.S. adults who used these drugs in 2008, and differences between genders and age groups. It does not suggest any rising epidemics in prescribing of benzodiazepines, as there is none. Indeed, prescribing of benzodiazepines for mood and anxiety disorders decreased in the U.S. between 2001 (90 mil prescriptions) and 2007 (85 mil prescriptions), while population had increased.

Regarding insomnia, Olfson et al (1) only echo some concerns raised in the past. They quote a 11 year old National Institute for Clinical Excellence (NICE) guidance (4) for the use of zaleplon, zolpidem and zopiclone (not benzodiazepines), recommending the use of hypnotics only on short-term basis for severe and impairing insomnia and only after careful consideration of nonpharmacological options. The recommendation of using nonpharmacological options is fine for brief, situational, intermittent insomnia. Yet, recommending only a short-term treatment for severe impairing insomnia is not clinically suitable. Insomnia is now considered a chronic disorder: its definition specifies duration of at least 3 months. In clinical practice, we usually do not treat chronic illness for a brief period of time. The requirement of only a brief use of hypnotics in insomnia was removed from most regulatory materials. Actually, we do not have enough long-term studies available. Some "long-term" studies (only 6 months) actually suggest that prolonged treatment with eszopiclone (5) and zolpidem (6) improves daytime concentration, work performance and patient satisfaction. Unfortunately, we do not have similar studies with benzodiazepines, but their long-standing use for this indication by clinicians suggests similar conclusions. Last but not least, the relationship between insomnia and depression is bidirectional (7), since untreated insomnia may lead to depression.

Benzodiazepines provide an effective treatment of anxiety disorders (8-10). Their use has been in part supplanted by selective serotonin reuptake inhibitors (SSRIs), interestingly without any supporting evidence of superior efficacy or better safety data. Indeed, when benzodiazepines and antidepressants were directly compared in controlled trials, a superiority of the former in both efficacy and side effect profile emerged (11). For instance, in Nardi et al's comparison of clonazepam vs. paroxetine in panic disorder (12,13), the benzodiazepine was not only faster and better during the short-term treatment, but remained effective in long-term (3 years) treatment, when tolerance developed to its sedative effect, while side effects of paroxetine such as sexual dysfunction and weight gain remained an issue. The original observation of non-responsiveness of panic disorder to benzodiazepines (in contrast to imipramine) was probably mainly due to the usage of subtherapeutic doses of those drugs.

The potentials for dependency, toxicity and abuse of benzodiazepines have been emphasized in the literature, yet the percentage of abuse is really low in relation to the number of people using them (14). Also, as Greenblatt et al (8) pointed out, since benzodiazepines do not cure neither anxiety nor insomnia, symptom recurrence can be anticipated after their discontinuation, and many critics may have mixed in their observations symptoms of withdrawal with recurrence of the anxiety disorder symptomatology.

Furthermore, the withdrawal phenomena that occur with SSRIs (15) and atypical antipsychotics (16) have been frequently ignored. In the case of SSRIs, these phenomena have been termed "discontinuation syndromes", but are in no way milder or less troublesome than those entailed by benzodiazepines (15).

Concerns have been also raised about relationships between benzodiazepines and events such as risk of falling and car accidents, and dementia (2,3). However, at least some of these relationships could be spurious (17), and it seems premature to conclude that benzodiazepines are a causative factor in a multidimensional disorder such as Alzheimer's disease. These concerns also ignore the fact that benzodiazepine side effect profile is in many aspects very favorable compared to the long-term use of SSRIs and antipsychotics. Unfortunately, the use of antipsychotics in generalized anxiety disorder has greatly increased in the U.S., as it seems that general practitioners falsely believe that these drugs are safer than benzodiazepines.

There have been also calls for more restrictions on prescribing benzodiazepines. More control and restrictions do not usually work well, as we have seen in the case of boxed warning about suicidality associated with antidepressants. Benzodiazepines are actually controlled substances under the Controlled Substances Act in the U.S.. Further regulation of prescribing benzodiazepines using so-called triplicate prescriptions was abandoned in some U.S. states after this regulation led to an increase in prescriptions of barbiturates, meprobamate and other more toxic medications.

Many concerns have been also raised about prescribing benzodiazepines for the elderly. However, as pointed out by Salzman and Shader, "experienced geriatric clinicians often find that judicious use of low-dose, short half-life benzodiazepines reduces stress, promotes daytime functioning, and assists in sleep onset; elderly patients themselves report that they would gladly forgo short-term memory reduction

in exchange for a calmer daytime and reliable sleep onset" (17, p. 2).

How and why did we get to our profession's negative view of benzodiazepines, a view which is not necessarily shared by other disciplines? A part of the problem is a different perspective by different clinicians. As noticed by Starcevic (10), clinicians working in settings for the treatment of substance use disorders tend to take a "harsh" stand on long-term use of benzodiazepines, while clinicians working with patients with anxiety and related disorders may be more willing to see the "good side". We would like to add that, unfortunately, when new medications are introduced, their "superior" profile is suddenly promoted and marketed, even if the evidence concerning their superiority to existing medications is unclear or not available, especially since comparison to a gold standard is no longer required by the U.S. Food and Drug Administration (FDA), and superiority to placebo is considered satisfactory.

It is worth mentioning that a provision in the U.S. Affordable Care Act that the pharmaceutical industry successfully defeated was the plan to compare efficacy of cheap vs. expensive medications. Is it possible that cheap benzodiazepines would fare better in anxiety disorders than some expensive new antidepressants and antipsychotics? We can probably guess the answer, but we would prefer systematic studies to be done.

In conclusion, clinicians know that benzodiazepines, like any other medications, are unlikely to entail permanent and definitive solutions to chronic anxiety states, insomnia and other conditions. However, as stated by Starcevic (10, p. 1283), "the likely reasons for their ongoing popularity include their consistent and reliable effectiveness for the most prominent symptoms of anxiety, relatively good tolerability, quick onset of action, possibility of using them on an 'as-needed' basis and the realization that the newer antidepressants have not been as useful for anxiety and related disorders as they had initially seemed to be".

Physicians should remain free to prescribe benzodiazepines like any other psychotropic medications. Suggesting simplistic measures for complex clinical issues is not an answer. Informed prescribing rooted in critical thinking is.

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Psychotropic drugs and homicide: a prospective cohort study from Finland

After a high-profile homicide case, there is often discussion in the media on whether or not the killing was caused or facilitated by a psychotropic medication. Antidepressants have especially been blamed by non-scientific organizations for a large number of senseless acts of violence, e.g., 13 school shootings in the last decade in the U.S. and Finland (1). In September 2014, there were more than 139,000 hits from Google for the search terms "antidepressant, homicide", and more than 1,050,000 hits for the terms "antidepressant, violence". It is likely that such massive publicity in the lay media has already led a number of patients and physicians to abstain from antidepressant treatment, due to the perceived fear of pharmacologically induced violence.

What is the scientific evidence for an association between psychotropic drugs and homicidal behavior? Most of the available studies are case reports that only suggest a coincidental link between violence or homicide and antidepressants (2,3) or benzodiazepines (4), while very little is known about the association between antipsychotics and homicide. Two recent ecological studies found no support for a significant role of antidepressant use in lethal violence in the Netherlands or the U.S., although data on individual offenders were not available (5,6). Quantitative data from the U.S. Food and Drug Administration (FDA) adverse event reporting system (7) imply that some antidepressants may be associated with a disproportionately high number of violent events (8). On the contrary, two small studies on antidepressant use among a special subgroup of homicide-suicide offenders found no evidence to support a causal link between antidepressants and homicidal behavior (9,10).

There are three crucial conditions that must be fulfilled to properly study the putative association between exposure (i.e., use of a psychotropic drug) and outcome (homicide): a) the sample must be unselected, to be representative of the total offender population; b) the reason for prescribing the medication must be considered and controlled, and c) the effect of other concomitant medication(s) must be adjusted. No such studies have been done thus far on the association between the risk of committing homicide and the use of psychotropic drugs.

We carried out a prospective cohort study with an embedded case-control design in order to test the hypothesis that current antidepressant treatment is associated with an increased risk of committing a homicide. We prospectively collected a database that included all homicides reported to, and investigated by, the police in Finland in the period 2003-2011 (11). From the 1091 homicides known to police, after exclusion of 12 cases not solved, 7 offenders coming from abroad, 24 offenders whose data were blocked due to security reasons, and 10 offenders excluded due to incomplete data on previous incarceration, we were left with 959 offenders, who were included in our analysis. For each offender, 10 population controls where picked from the Population Information System by matching individuals by gender, age (year of birth), and home municipality at the time of each homicide.

Information on medication use from January 1995 to December 2011 was obtained for all cases and their controls through record linkage to the nationwide Finnish Prescription Register. The database contains the date of prescription purchase, the Anatomic Therapeutic Chemical (ATC) code, and the purchased quantity, stated as the number of defined daily doses (DDDs), which are defined by the World Health Organization (12). This procedure has been described in more detail in our previous cohort studies (13-16).

We identified a subject as a "current user" if (s)he was using a given drug at the time of the homicide/matching, according to the amount of medication purchased in DDDs. Drug exposure was assumed to start at the date of purchase, and drug exposure duration was determined by the amount of DDDs. Previous use (Yes/No) was also based on the date of purchase and amount in DDDs. A subject had previous use if (s)he made a prescription purchase during the previous 7-year period, before the time of homicide/matching, but the drug exposure ended before the date of homicide. Among those offenders who had been in prison during the 7-year period prior to homicide, the time during their prison sentence (prior to their release) was censored, and also among their matched control subjects. Subjects aged 25 years or younger were further investigated in a separate analysis.

The primary outcome measure was the risk of offending during current use vs. no current use for three major categories of psychotropic medications: antidepressants, benzodiazepines, and antipsychotics. Within the offender cohort, each individual served as his/her own control. In this analysis, individuals without any medication exposure were omitted. A Poisson regression model was used to estimate the relative risk (RR) of homicide during current use versus no-use of each study medication among the offenders.

The follow-up time on medication was based on DDDs, and truncated to each person's total follow-up time. The RR was calculated for both the adjusted and unadjusted models, according to age, gender, current use of illegal drugs, current use of alcohol, and both current (i.e., at the time of the homicide) and previous use of other study

medications. When comparing offenders and matched controls, the odds ratio (OR) was used as a measure for the risk, and it was estimated using the conditional logistic regression model that takes into account the matching sets (which individuals served as controls for each offender).

For primary outcome measures, the level of statistical significance was set to $p<0.016$ to account for multiple testing (Bonferroni correction). The secondary analysis compared the current vs. no current use of seven other medication categories (opioid analgesics, other analgesics, antiepileptics, lithium, stimulants, medicines used in addictive disorders, other anxiolytics), which were used as covariates in the primary analysis. The level of significance in the secondary analysis was set to $p<0.005$.

The median age of offenders and controls was 36.3 years (range 13.3-88.0 years). A total of 849 (88.5%) offenders were males, and 42 (4.4%) had more than one victim, 761 (79.4%) were intoxicated by alcohol and 51 (5.3%) by illicit drugs during the offence (as confirmed by the police).

The analysis within the offender population revealed that the adjusted RR was 1.31 (95% CI: 1.04-1.65; $p=0.022$) for current use vs. no current use of antidepressants, 1.45 (95% CI: 1.17-1.81; $p=0.001$) for current use vs. no current use of benzodiazepines, and 1.10 (95% CI: 0.82-1.47; $p=0.54$) for current use vs. no current use of antipsychotics. The current use of both opioid (1.92; 95% CI: 1.36-2.72, $p<0.001$) and non-opioid (3.06; 95% CI: 1.78-5.24, $p<0.001$) analgesics was associated with significantly increased risk of offending. Among subjects aged 25 or younger, the only findings approaching statistical significance were observed for current use of opioid analgesics (adjusted RR 3.23; 95% CI: 1.05-9.94; $p=0.04$) and benzodiazepines (adjusted RR 1.95, 95% CI: 0.95-4.00, $p=0.07$). No significant interactions were observed between current use of psychotropic medications vs. intoxication by alcohol or illicit drugs.

The analysis based on case-control design showed an adjusted OR of 1.30 (95% CI: 0.97-1.75) as the risk of homicide for the current use of an antidepressant, 2.52 (95% CI: 1.90-3.35) for benzodiazepines, 0.62 (95% CI: 0.41-0.93) for antipsychotics, and 2.16 (95% CI: 1.41-3.30) for opioid analgesics.

The results of this prospective study show that antidepressant use *per se* was associated with an only modestly increased risk of committing a homicide, with borderline statistical significance. Benzodiazepine and analgesic use was linked with a higher risk of homicidal offending, and the findings remained highly significant even after correction for multiple comparisons.

These results – which may probably be generalized to other developed and stable societies that have a low to medium homicide rate, although not necessarily to countries with higher rates of organized and premeditated crime – imply that the use of antidepressants should not be denied to either adults or adolescents due to a presumed risk of homicidal behavior. The surprisingly high risk associated with opioid and non-opioid analgesics deserves further attention in the treatment of pain among individuals with criminal history.

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Designer benzodiazepines: a new challenge

In the February 2015 issue of *World Psychiatry*, Schifano et al (1) gave an overview of novel psychoactive substances and their potentially harmful effects. They highlighted that in the last couple of years the number of drugs offered via Internet shops has increased dramatically and that benzodiazepines are often used to treat intoxications with these drugs in the clinical setting.

We would like to point out that designer benzodiazepines have become a rapidly growing class of drugs of abuse in their own right in the last two years. We believe that mental health professionals should be aware of this new development.

The first designer benzodiazepines available online were diclazepam, flubromazepam and pyrazolam (2-4). Recently, five others became readily available (i.e., clonazolam, deschloroetizolam, flubromazolam, nifoxipam and meclonazepam), none of which has been approved for medicinal use in any country. Nearly all of these compounds have been synthesized as drug candidates by pharmaceutical companies and their syntheses, as well as basic animal testing data, are described in the literature along with many more potential successors (5). Typical formulations are tablets, capsules or blotters in various doses. Furthermore, the drugs are also offered as pure powders with prices as low as 5-10 US cents per dose.

Immunochemical tests applied in clinical settings and drug rehabilitation detect most of the designer benzodiazepines with sufficient sensitivity. However, the mass spectrometric methods needed for confirmation do not regularly cover the latest designer benzodiazepines, due to lack of reference materials. Practitioners should be aware of this limitation and carefully assess seemingly "false-positive" results.

Due to their high potency, compounds like clonazolam or flubromazolam can cause strong sedation and amnesia at oral doses as low as 0.5 mg. Such low doses are extremely difficult to measure for users handling bulk materials, and tablets often vary greatly in the content of the active ingredient. This can lead to unintended overdosing, and could also be of concern in drug facilitated crimes (6).

Designer benzodiazepines are often taken as "self-medication" by users of stimulant and hallucinogenic drugs, leading to "upper downer cycles" (7) and risk of severe addiction in people frequenting the party scene. Persons with anxiety disorders also tend to self-medicate on these drugs if a medical prescription cannot be obtained (8). The high availability of these drugs via online vendors and the low price may facilitate development of addiction in this population.

Many "classical" benzodiazepines are listed in Schedule 4 of the 1971 United Nations Convention. They are also in Schedule IV of the U.S. Controlled Substances Act, but it is unclear if designer benzodiazepines are covered by the Controlled Substances Analogue Enforcement Act, 1986. Similar legal problems exist in most other countries in the world, making it difficult to reduce availability of these dangerous new drugs.

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When local poverty is more important than your income: mental health in minorities in inner cities

In the next decades, the world's population in urban areas will increase by 2-3 billion people (1). Within this population context, there is increasing evidence that both socially disadvantaged inhabitants and people with a minority status are at high risk for mental disorders and mental health burden (2-4).

Differential analyses of individual-level and neighborhood-level socioeconomic factors in native citizens have suggested that the neighborhood context may impact mental health beyond individual differences in income and education (5). Recent data indicate that the processing of social stress is different in migrants in connection with urbanicity, raising the possibility of additive or interactive effects of these risk factors (6). We investigated the effects of individual differences in socioeconomic and minority status, as well as of poverty and ethnic composition at the level of urban neighborhoods, on mental health in an inner city population in Berlin, Germany.

Participants were selected from public registries comprising all residents in 11 neighborhoods within the central district of Berlin's inner city ("Berlin-Mitte") in combination with on-site selection and snowballing (see 7 for details). We focused on the largest minority in Berlin, i.e., people with a Turkish migration background (8). Respondents ($N = 478$) reflected the average age and gender distribution within each of the neighborhoods (8). Neighborhood variables derived from microcensus data included the age and gender distribution, the proportion of residents with minority status (ethnic density), and the proportion of residents on public welfare in local neighborhood communities.

Interviews were conducted in German and Turkish by trained interviewers and consisted of a socio-demographic assessment and the General Health Questionnaire 28-item version (GHQ-28) (9).

We used individual level variables (age, gender, years of education, monthly net income per household member, and minority status) and neighborhood-level variables (ethnic density and percentage of residents on public welfare within a neighborhood) to predict mental health status in a multilevel model using R System for Statistical Computing (www.cran.org). In addition, we specified a term for the interaction of the presence of a migration background with local poverty levels, which we added to the specified models.

On average, subjects with a minority status had significantly less years of education, less income, and higher levels of mental distress. On an individual level, increasing age ($\beta_i = 0.15$, $SE = 0.07$, $p < 0.05$), decreasing income ($\beta_i = -0.86$, $SE = 0.42$, $p < 0.05$), and minority status ($\beta_i = 3.58$, $SE = 1.78$, $p < 0.05$) were associated with an increase in mental distress. The most pronounced effect due to individual factors was associated with having a migration background, which led to an increase of more than 3.5 points on the GHQ-28. The age effect corresponded to an increase of roughly 1.5 points on the GHQ-28 per decade, and each 100 Euros lower monthly income led to an increase of roughly 1 point on the GHQ-28.

When assessing neighborhood effects, the percentage of citizens on public welfare at the neighborhood level accounted for the largest share in the variance in mental health ($\beta_n = 1.12$, $SE = 0.26$, $p < 0.001$), corresponding to roughly 11 points on the GHQ-28 for each 10% increase in the percentage of residents receiving public welfare benefits within the neighborhood. Crucially, we found a significant interaction between individual minority status and neighborhood level poverty at a more liberal threshold ($\beta_{i,n} = 0.50$, $SE = 0.30$, $p < 0.10$), indicating that a 10% increase in the percentage of residents on public welfare in the neighborhood corresponded to an increase of roughly 8 points on the GHQ-28 in the entire population, and an additional 5 points on the GHQ-28 in residents with minority status.

To the best of our knowledge, this is the first study showing that poverty in the neighborhood, as indexed by the proportion of residents in a local neighborhood on public welfare, explains significantly more variance in mental health among persons with versus without a migration background, beyond individual effects of age and income.

From a public health perspective, these findings may have implications for the prevention of mental health problems in inner city minority populations. One may well hypothesize that general economic measures and interventions aimed at alleviating poverty may, on a population level, have a significant impact on mental health. Likewise, interventions aimed at alleviating the mental health burden specific to residents with a minority status may have to take local poverty effects into account. At this level, policy makers, public health experts, and actors in community psychiatry and prevention may want to consider expanding service provision according to local economic factors.

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Urbanization and the prevalence of schizophrenia in China between 1990 and 2010

Among the environmental risk factors for schizophrenia, evidence supports a role of urbanicity (1-3). In recent decades, urbanization has been occurring at a massive scale in low- and middle-income countries (4,5). It is therefore of global public health importance to explore how rapid urbanization might have affected the burden of schizophrenia in growing economies, with China being a prime example.

Epidemiological evidence in China has improved over the past two decades and Chinese academic journals have become accessible in electronic databases (6). Moreover, China recently underwent urbanization and economic development at an unprecedented scale: 26.4% of its 1.1 billion inhabitants lived in urban areas in 1990, rising to 49.2-49.7% of 1.3 billion in 2010 (4,7). We may expect a significant increase of schizophrenia burden in China as a result.

To explore this, we conducted a systematic review of the Chinese and English literature, through China National Knowledge Infrastructure, Wanfang and PubMed, for the years from 1990 to 2010. Only studies that had applied a case definition based on DSM-III or IV, ICD-9 or 10, or Chinese Classification of Mental Disorders (CCMD-2, 2R or 3) were retained.

Based on pre-defined minimum quality criteria, 42 prevalence studies were selected. They were mostly large population-based studies, typically using a two-stage data collection design in which trained assessors performed an initial screening and psychiatrists followed up with a detailed evaluation. Direct contact was made with the corresponding authors of 13 studies to obtain any missing information. Geographically, the retained studies covered 21 of mainland China's 31 provinces, municipalities and autonomous regions. Bayesian methods were applied to predict maximum likelihood for point prevalence and lifetime prevalence in urban and rural China in the years 1990, 2000 and 2010.

The analyses of the 42 studies combined information from 2,284,957 people, 10,506 of whom were diagnosed with schizophrenia in their lifetime. In urban areas, the point prevalence ($\geq$15 years) of the disorder was 0.32% (95% CI: 0.29-0.36) in 1990, 0.47% (95% CI: 0.44-0.50) in 2000, and 0.68% (95% CI: 0.57-0.81) in 2010. In contrast, in rural areas, the corresponding estimates were 0.37% (95% CI: 0.33-0.42), 0.36% (95% CI: 0.35-0.38), and 0.35% (95% CI: 0.33-0.38). Lifetime prevalence ($\geq$15 years) in urban China was 0.39% (95% CI: 0.37-0.41) in 1990, 0.57% (95% CI: 0.55-0.59) in 2000, and 0.83% (95% CI: 0.75-0.91) in 2010. The corresponding estimates for rural areas were 0.37% (95% CI: 0.34-0.40), 0.43% (95% CI: 0.42-0.44), and 0.50% (95% CI: 0.47-0.53).

Applying these prevalence estimates to the corresponding population of China, there were 3.09 (95% CI: 2.87-3.32) million persons affected during their lifetime in the year 1990. Twenty-seven percent of the cases were from urban areas, which corresponds to the overall proportion of urban residents in China in the same year (26.4%). By 2010, the number of persons affected with schizophrenia rose to 7.16 (95% CI: 6.57-7.75) million, a 132% increase, while the total population of China only increased by 18% during this period (4). Moreover, the contribution of expected cases from urban areas to the overall burden increased from 27% in 1990 to 62% in 2010, well above the proportion of urban residents in China in 2010 (49.2-49.7%).

This study helps to establish the universality of urbanicity as a risk factor and the extent to which it affects the burden of schizophrenia in a large country that underwent rapid urbanization. As schizophrenia prevalence was found to be similar in rural and urban China at the beginning of industrialization (late 1980s) (8), our findings suggest that the mechanisms driving the risks of illness in urban areas are likely to be associated with modern urban lifestyles. The lower rates of schizophrenia found when China was less industrialized are consistent with studies that reported lower rates of the illness in low- and middle-income countries (3).

This analysis has broad implications. Many populous parts of the world, particularly in low- and middle-income countries, are undergoing urbanization at a scale and rate that took Western countries centuries to achieve (9). Global urbanization may therefore result in an increased global prevalence of schizophrenia through mechanisms that need to be further explored.

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Obituary: Juan José López-Ibor (1941-2015)

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In 1966, Juan José López-Ibor's father hosted the 4th World Congress of Psychiatry in Madrid. I listened to him speaking and was amazed by the width of his knowledge and the cosmopolitan style which he adopted with ease, while remaining harmonious with the traditions and culture of Spain.

Juan José tried to emulate his father in the choice of his profession, in his international links, in the topics which he selected for study (such as psychopathology), in his loyalty to and work in the WPA (of which he became President on the thirtieth anniversary of his father being elected President) and in numerous other ways. He also admired his mother, an accomplished scholar and devoted mother to him and his eleven brothers and sisters, and a person whose wisdom continued to influence his later career and action.

Yet, while trying to emulate his father, Juan José surpassed him. A unique and remarkable person, he made major contributions to psychiatry, to medicine in general and to science, established a worldwide network of friends and collaborators, and educated generation after generation of psychiatrists and medical students.

Fluent in major European languages and superbly trained in psychiatry in Germany, France, Switzerland and Spain, he accumulated knowledge and experience about a broad variety of subjects, ranging from philosophy to ecology and from psychoanalysis to neuroimaging. He could speak about a great variety of topics, gracing the arrays of facts with anecdotes and personal views, making his talks resemble a Christmas tree with candles illuminating some of the branches and with many surprising adornments that made you want to hear more and more.

All of these features gained strength and meaning from the humanism that was at all times a dominant determinant of Juan José's action and thought. He acted in consonance with his convictions and profound sense of justice, fighting for the rights or people with mental illness and against the abuse which they so often experienced. He did so with strength but also with a clear determination to improve the situation rather than stop at punishing those who were responsible for the situation that needed to be improved. A good example of the implementation of this attitude was the improvement of training programs for psychiatrists that resulted from the highly successful visit of a WPA group to China at the time of Falun Gong members' complaints about the way in which the members of the sect were treated and considered mentally ill. His support and contribution to the development of the Madrid Declaration, which governs the professional behavior of psychiatrists, is another example of his commitment to justice and ethical practice of medicine.

I had the pleasure of working with Juan José over many years – first while we developed collaborative ventures between the mental health program of the World Health Organization and Juan José's department (and his local and international network) and subsequently during many years of joint work in the WPA. The project of making the mental disorders chapter of the International Classification of Diseases (which he and his coworkers translated into Spanish) widely used exemplified Juan José's remarkable capacity to organize the translation of knowledge into practice.

He made arrangements for the then new classification to be presented in a series of scientific meetings all over the country, ensured that printed copies were made available to all, designed training programmes in the use of the classification for different categories of mental health workers, spoke about it at various major professional meetings, both in Spain and in other Spanish speaking countries. The program was so successful that it became the model for the introduction of similar changes into practice in a number of other mental health programs in different countries.

Several years ago Juan José was struck by an illness that did not respond to treatment and eventually took him away from us. He understood that the prognosis of his ailment was poor and that his days were numbered. His reaction to this realization was admirable. He continued with his work, attended scientific meetings, wrote about various subjects and above all retained his capacity to laugh and be jovial, pleasant in company and admirable in his abilities. His way of dealing with his illness was yet another confirmation of greatness given only to a few.

It would be easy to list the many programs and projects in which Prof. López-Ibor played a major role and recall the topics of his many publications and presentations. I did not do this because I believe that the most important legacy that he left is that of being an example of a person who has reached the peak of professional capacity yet retained and continued demonstrating his humanism, sense of justice and commitment to ethical principles that should govern our profession.

I shall miss him, not only as a model from which one can always learn and be inspired, but also as a good friend always caring and optimistic, courageous and witty, generous and thoughtful.

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WPA – Social justice for the mentally ill

Dinesh Bhugra
President, World Psychiatric Association

I am truly honoured and humbled to take this role on. Nearly nine months into the job, I am realizing how much hard work my predecessors had put in over the years and would like to thank them for their input and efforts into making the organization what it is.

Following the publication of the WPA Action Plan 2014-2017 in the October 2014 issue of *World Psychiatry* (1), it is worth recalling that the General Assembly in Madrid approved this programme, which aims to highlight the public mental health agenda. Its themes form the core of social justice for people with mental illness. The aim is to improve the outcomes and chances for recovery.

There is no reason why people with mental illness should die 15-20 years younger and face discrimination and prejudice. Five parallel themes have been identified. These include: a) domestic gender-based interpersonal violence; b) child sexual, physical and emotional abuse; c) prisoner mental health care; d) mental health care of underserved groups such as elderly; lesbian, gay, bisexual and transgender; those with intellectual disabilities, migrants, refugees and asylum seekers; and e) mental health promotion for all.

Although these five streams are vertical, they also form a horizontal basis and for each of them a Presidential Task Force has been appointed. The details of the Task Forces are available from me directly or the WPA Secretariat. The aim is to launch reports at international conferences. If any individual or group wishes to take part in this, please do not hesitate to contact the Secretariat.

For the first time ever, the World Economic Forum has appointed a Global Agenda Council on Mental Health and this gives me a unique opportunity to work with a number of key stakeholders to develop and deliver the agenda on mental health. The WPA is working very closely with the World Health Organization to develop and deliver this mental health agenda. I was invited to speak at the H20 Health Summit in Melbourne as a prelude to the G20 summit in Brisbane and I strongly believe that around the globe we are reaching a point where mental health is being taken seriously. We all have a role to play and once again I would strongly urge you to contact your policy makers making sure that often it is other stakeholders such as Ministers for Education, Economy or Employment who may be more interested in getting families back to work.

There are examples from other countries which we can attempt to emulate. But the key to all this is social justice. Social justice means that patients with mental illness should have the same rights to employment, housing, social functioning and outcomes and recovery as those who have physical illness.

The WPA website is under renovation and reconstruction with an attempt to make it more interactive and user-friendly. I have also established a Presidential Task Force to develop social media presence for the organization. Another Presidential Task Force has been established on public education and I am delighted that A. Sharma from India is leading it. A. Tasman is leading the Presidential Task Force on setting up a qualification in collaboration with our collaborating centres and university partners. I am determined to get more early career psychiatrists involved in various committees and activities of the WPA and as agreed by the Executive Committee they will have observer status on all standing and operational committees.

The new Executive Committee has had two meetings since the election and we are all keen to work together to provide added value to the member organizations of the WPA at a number of levels.

As you know, Prof. Juan José López-Ibor passed away on January 12, 2015. He was a true giant of Spanish psychiatry and of world psychiatry. The Executive Committee and the whole organization will miss him. His contributions will be part of his legacy and will form a part of the global psychiatry for decades to come. We are all immensely grateful that he contributed so much to psychiatry research, policy and development at a number of levels. On a more personal level, I am really grateful for his support, help and friendship and we shall miss his sage advice. Our thoughts are with his family and friends and may his soul rest in peace.

Before the recent WPA Regional Meeting in Hong Kong, I had the opportunity of meeting the Secretary for Health as well as the Secretary for Social Care to discuss what changes are needed to improve services in Hong Kong. I have had similar meetings in the UK. In the recent Indian Psychiatric Society annual meeting, some of the most exciting research and work that is going on in India and in the region was presented. These observations illustrate that there is an opportunity where we should be learning from each other about what is the best practice for our patients.

Preparations are underway for the International Conference of the WPA in Bucharest and a Regional Meeting in Osaka and I very much hope that as many members as possible will attend these so that we can continue to learn from each other.

I am keen to hear from our members and societies about what the added value of the WPA is. So please do feel free to get in touch with ideas on how we can improve the organization and communication both within the organization and with other agencies.

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An update on the activities of WPA Scientific Sections

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WPA Secretary for Sections

Scientific Sections keep on having a prominent position in the working of WPA, especially for promoting and disseminating scientific knowledge around the globe. The current number of Sections has increased to 69, after the establishment of the new Section on HIV/AIDS Psychiatry, chaired by M.A. Cohen.

WPA Sections enjoy a great degree of independence within the framework of the WPA Statutes and By-Laws (1,2). The Section work is supported by an Operational Committee headed by the Secretary for Sections.

During the 2014 World Congress of Psychiatry in Madrid, Section officers attended a special meeting, during which reports were presented about the activities implemented during the triennium 2011-2014. The results of a WPA survey showed that the majority of Sections were fully functional during that period. Organizing sessions at WPA sponsored and co-sponsored meetings was found to be the most common activity (implemented by 88% of Sections). There was also a noticeable increase in the number of WPA co-sponsored meetings organized by individual Sections during 2011-2014. The number of such WPA co-sponsored meetings and conferences (either organized as an independent meeting and/or supported by one of the WPA Scientific Sections) reached a very high number (39 meetings compared to 17 meetings in the triennium 2008-2011). Within the World Congress, 65 symposia and 22 workshops were organized by Sections.

Some Scientific Sections have produced position statements during the triennium (e.g., that on independent medical examinations by the Forensic Psychiatry Section), and others have developed training courses for residents (e.g., that developed by the Section on Religion, Spirituality and Psychiatry).

Several Sections also have officially linked international scientific journals. These include the *Journal of Affective Disorders*, *Psychopathology*, *Academic Psychiatry*, *History of Psychiatry*, *Personality and Mental Health*, the *Journal of Mental Health Policy and Economics*, the *International Journal of Mental Health*, the *Journal of Intellectual Disability Research*, *Activitas Nervosa Superior*, *Psychiatry in General Practice*, *Transcultural Psychiatry*, and the *Archives of Women's Mental Health*.

The survey also revealed that WPA membership have considerable information on the activities of the WPA Scientific Sections, and 60% of the responding Member Societies rated the impact and visibility of these activities as "excellent" or "good", while the quality of these activities was rated as "excellent" or "good" by 65% of the respondents.

The WPA Action Plan for 2014-2017 (3) was also discussed during the Madrid meeting, with a special emphasis on Sections' future role in developing the theme of promotion of mental health as a targeted action. Sections have indeed started planning various activities looking at a number of aspects of this particular area, with a main focus on producing educational leaflets for the general public, updating the WPA website, preparing slides and educational material for professionals, developing slides and educational material for medical students, providing suggestions for curriculum development for trainees in psychiatry, producing guidelines and consensus statements, organizing scientific sessions at WPA meetings, identifying themes for intersectional collaboration, implementing some joint intersectional projects, and strengthening links with other allied professional organizations.

The Sections also keep on having their elections every three years, and it is heartening to note that most of them have elected new members on these positions. This will certainly help WPA in promotion of leadership and involvement of young psychiatrists in the working of the Association.

There will be a prominent participation of Scientific Sections at the forthcoming WPA International Conference in Bucharest (June 2015). An Intersectional Forum is also planned there on the topic of old age psychiatry, and two intersectional educational teaching and training programmes will also take place.

Section officers and members are also contributing extensively to the WPA official journal *World Psychiatry* (4-18). Their interest and participation in the development of the chapter on mental disorders of the ICD-11 is another ongoing contribution to the psychiatric field (19,20).

It is expected that the enthusiasm of Scientific Sections for their WPA work will continue and will bring further contributions to the quality of scientific knowledge and the development of innovative approaches in psychiatric practice.

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