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The WPA is an association of national psychiatric societies aimed to increase knowledge and skills necessary for work in the field of mental health and the care for the mentally ill. Its member societies are presently 135, spanning 118 different countries and representing more than 200,000 psychiatrists.

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Further information on the WPA can be found on the website www.wpanet.org.

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Social neuroscience as an ideal basic science for psychiatry

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It has been often stated (e.g., 1) that we human beings live "in two worlds": a world of biology and physical causes, to which our brain also belongs, and a world of meanings, symbols, discursive contexts and interpersonal relationships.

Each of these worlds has its own processes and laws, which can be studied separately and have indeed been studied separately for several centuries. On the one hand, there is the domain of neurosciences, in which the brain has frequently been studied as a "biological machine", isolated from social influences. On the other, there is the domain of social sciences, in which the world of human relationships has usually been explored ignoring brain processes, as if they were totally irrelevant (2).

Psychiatry, and in general the issue of mental disorders, has been put in the middle by this dualism. Neurobiological and psychosocial views of mental disorders have confronted each other for many decades, not only in the scientific and lay literature, but also in the perception of people with those disorders, who often conceptualize their problems in either essentially biological or essentially psychosocial terms (3). The specificity of psychiatric expertise and the need for a specific psychopathological language and discourse have been often put in question, and psychiatry has recurrently been warned either to become a "clinical neuroscience", replacing descriptive psychopathology by neurobiological and behavioral measures, because mental disorders are indeed "brain diseases" (e.g., 4), or to adopt a psychosocial paradigm, conceptualizing mental disorders in terms of understandable responses to adverse environmental situations or problematic interpersonal relationships (e.g., 5).

That the above two worlds do exist, that they can be studied separately, and that they cannot be reduced to each other, or fully explained each through the concepts that are specific to the other, there seems to be no doubt. But that they are independent from each other appears today implausible. The existence of the world of meanings, symbols and interpersonal relationships in which we human beings are immersed is only made possible by the complexity of our brains.

The brain processes involved in the implementation of several aspects of social behavior (for instance, the generation and reception of facial and non-facial social signals; the perception and understanding of others' mental states; the self-regulation of emotions in social contexts; the development and maintenance of social bonds) are now being elucidated (e.g., 6-9). Furthermore, it is now clear that, not only brain damage or dysfunction can affect social behavior, but early social experiences can affect the development, structure and functioning of the brain, thereby conditioning the individual's subsequent response to social events (e.g., 10).

Most mental disorders are likely to emerge from a dynamic interplay between the above "two worlds", so that, not only neither neural dysfunctions nor problematic interpersonal relationships can fully "explain" those disorders, but even identifying what is "primary" and what is "secondary" may often be a useless and misleading exercise.

This is why the interdisciplinary area of social neuroscience is of such a great importance and interest for psychiatry, arguably being the "basic science" which most closely fits the integrative nature of psychiatry as a clinical discipline. And this is how what has been for centuries a reciprocal disdain and sometimes a polemic confrontation between neurosciences and social sciences as applied to psychiatry may become now a fruitful interaction, generating new models and research instruments, as well as new intermediate phenotypes, and possibly contributing to overcome the current stagnation in the development of new psychiatric interventions.

We human beings are "embodied subjects", i.e. our existing as objects (or bodies, including brains) in a physical world and as subjects in an interpersonal world are inextricably interlinked (11). As a consequence, mental disorders require an interdisciplinary research frame (exemplified by social neuroscience) and an integrative clinical expertise (provided by psychiatry).

The fact that we are "embodied subjects" is of course relevant not only to psychiatry, but to the whole of medicine. Physical diseases, even if unequivocally located in the body, may often have an interpersonal component in their determination, manifestations and course. This component may need to be recognized in clinical assessment, taken into account in management (as well as in interpreting treatment response), and explored through research informed by social neuroscience (e.g., study of reappraisal of aversive emotional events in people with cardiovascular disease).

In this light, psychiatry may cease to represent an "exception" in the realm of medicine, and even become a "model" on which to reflect and from which to learn.

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WHO's Mental Health Action Plan 2013-2020: what can psychiatrists do to facilitate its implementation?

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Adoption of the Comprehensive Mental Health Action Plan 2013-2020 by the World Health Assembly in May 2013 provides the clearest example to date of the increasing commitment by governments to enhance the priority given to mental health within their health and public policy.

The fact that all countries – large and small, rich and poor, and from all regions of the world – have agreed on a common vision for mental health along with objectives to reach defined targets within a specified time period, gives ample testimony to the strength of current political commitment for mental health across the world.

This paper briefly introduces World Health Organization (WHO)'s Mental Health Action Plan 2013-2020 (the Plan) (1) and proposes some activities by psychiatrists that can facilitate its implementation.

THE PROCESS OF DEVELOPING THE PLAN

The Plan was developed as a direct consequence of a discussion by the World Health Assembly in May 2012 on global burden of mental disorders and the need for a comprehensive, co-ordinated response from health and social sectors at the country level.

The Assembly requested WHO to develop the Plan in collaboration with international, regional and national non-governmental organizations. WHO consulted a very large number of diverse stakeholders to develop the draft Plan; the WPA as well as a number of national psychiatric associations played an active role in providing inputs to the various drafts of the Plan. This not only ensured that the Plan covered all the areas considered important by various stakeholders but also increased their commitment to contribute to the implementation of the Plan.

A background technical paper on vulnerabilities and risks for mental health (2) was published to facilitate the drafting of the Plan. The World Health Assembly considered the draft Plan and adopted it in May 2013. This being the first formal Action Plan dedicated to mental health in the entire history of WHO, it can be considered a landmark.

THE CONTENTS OF THE PLAN

The Plan is organized around a vision, a goal, cross-cutting principles, objectives and actions, followed by a set of indicators and targets to be achieved in 8 years (1).

The vision of the Plan is ambitious: a world in which mental health is valued and promoted, mental disorders are prevented and in which persons affected by these disorders are able to access high quality, culturally appropriate health and social care in a timely way to promote recovery and exercise the full range of human rights to attain the highest possible level of health and participate fully in society free from stigma and discrimination.

The Plan relies on a number of cross-cutting principles: universal access and coverage, human rights, evidence-based practice, life course approach, multisectoral approach and empowerment of persons with mental disorders and psychosocial disabilities.

The Plan focuses on four key objectives: to strengthen effective leadership and governance for mental health; to provide comprehensive, integrated and responsive mental health and social care services in community-based settings; to implement strategies for promotion and prevention in mental health, and to strengthen information systems, evidence and research for mental health.

Each of these objectives is supported by a number of specific actions by member states, WHO and international and national partners. For example, objective 2 on services involves five actions: service reorganization and expanded coverage, integrated and responsive care, mental health in humanitarian emergencies, human resource development and addressing disparities. In addition to the broad actions, a number of options for implementation are given to suit countries in very diverse situations in terms of their health systems and resource availability.

The Plan includes a set of six targets to measure global progress in its implementation. Examples of targets include 20% increase in service coverage for severe mental disorders and decrease in rate of suicide by 10%. Countries are expected to develop their own national targets to contribute to the achievement of global targets.

WHO is collecting data in 2014 from each of the 194 member states on the core set of indicators and will publish these as the Mental Health Atlas 2014. Having already published similar atlases in 2001, 2005 and 2011 (3), as well as more than 80 country profiles based on WHO-AIMS (4), some comparisons across time will be possible on global, regional and national levels.

WHAT CAN PSYCHIATRISTS DO TO FACILITATE THE IMPLEMENTATION OF THE PLAN?

As members of professional associations

The WPA, representing more than 200,000 psychiatrists from all across the world, can facilitate the implementation of the Plan in a substantial way. The objectives of WPA include the improvement of care for the mentally ill, the prevention of mental disorders, the promotion of mental health and the preservation of the rights of mentally ill persons (5). These are very clearly aligned to the goal and objectives of the Plan. WPA had also worked closely with WHO in the preparation of the Plan. A strong support by WPA and its 135 member associations in the implementation of the Plan will go a long way in ensuring quick progress within countries.

Specific actions for international and national partners have been identified in the Plan; these can provide a template to build further collaboration between WPA, its member associations, governments and WHO. Support from professional associations such as WPA is especially needed in development of progressive national policies and legislations, mental health service reorganization including task sharing with non-specialized care providers and protecting human rights of persons with mental disorders in conformity with international and regional human rights instruments. Special attention should be paid to the needs of low and middle income countries, where the technical and financial resources are particularly scarce.

As leaders of mental health in their countries

Psychiatrists are often in prominent positions within the ministries of health or in academic centres. They often are the leaders and champions for mental health within countries. If they are better informed on the Mental Health Action Plan and the commitments that the government has made internationally, they can be more effective in their advocacy and leadership role. This may include, as appropriate, developing a national plan, raising resources and developing a multidisciplinary coalition for mental health.

As service providers

The Plan has clear directions on essential elements of health and social service provision as well as suggestions on utilization of the available human resources to deliver these services in an efficient manner. As essential members of service delivery teams, psychiatrists can facilitate efficient utilization of the available resources, especially those of relatively less specialized health care providers, including general doctors, nurses and health care workers. This involves task sharing and support and supervision by psychiatrists. This can facilitate enhancing service coverage while still maintaining a satisfactory quality of care.

As teachers and trainers

Psychiatrists are involved in education and training of doctors, nurses and mental health professionals, including psychiatrists. These training curricula often are antiquated and do not correspond well to the current state of evidence. The Plan, along with accompanying WHO clinical guidelines (6), can provide suitable training material. Elements of policy and service organization should also form a more substantial component of the training, since these skills are essential for the public health role that many psychiatrists will need to play.

As researchers

Mental health research output from most low and middle income countries is far too low (7), given the need for evidence-based practice and policy. The Plan envisages the collection of essential information, the evaluation of programmes and the conduct of research, especially on mental health services within countries. Psychiatrists can conduct and coordinate these activities to facilitate implementation of national plans and achievement of their objectives in line with the global Plan.

CONCLUSIONS

The Comprehensive Mental Health Action Plan 2013-2020 has paved the way for a new approach in mental health emphasizing community based care, a recovery approach and full respect of the human rights of people with mental and psychosocial disabilities.

Political commitment to this approach has been endorsed at the highest level by Ministers of Health, but is in stark contrast to the reality on the ground. Psychiatrists, as key leaders of mental health in their country, have a major role and responsibility to change the current situation through re-alignment with the goals, principles and objectives of the Plan.

The ambitious 2020 targets for mental health are possible but will require psychiatrists to embrace this new approach, working collaboratively with other mental health professionals, academia and civil society groups.

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SPECIAL ARTICLE

Taking the long view: an emerging framework for translational psychiatric science

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Understood in their historical context, current debates about psychiatric classification, prompted by the publication of the DSM-5, open up new opportunities for improved translational research in psychiatry. In this paper, we draw lessons for translational research from three time slices of 20th century psychiatry. From the first time slice, 1913 and the publication of Jaspers' General Psychopathology, the lesson is that translational research in psychiatry requires a pluralistic approach encompassing equally the sciences of mind (including the social sciences) and of brain. From the second time slice, 1959 and a conference in New York from which our present symptom-based classifications are derived, the lesson is that, while reliability remains the basis of psychiatry as an observational science, validity too is essential to effective translation. From the third time slice, 1997 and a conference on psychiatric classification in Dallas that brought together patients and carers with researchers and clinicians, the lesson is that we need to build further on collaborative models of research combining expertise-by-training with expertise-by-experience. This is important if we are to meet the specific challenges to translation presented by the complexity of the concept of mental disorder, particularly as reflected in the diversity of desired treatment outcomes. Taken together, these three lessons – a pluralistic approach, reliability and validity, and closer collaboration among relevant stakeholders – provide an emerging framework for more effective translation of research into practice in 21st century psychiatry.

Key words: DSM, RDoC, ICD, psychiatric classification, mind and brain, social sciences, reliability, validity, collaborative research, expertise-by-experience, values-based practice

(World Psychiatry 2014;13:110–117)

"A classification – N. Sartorius wrote back in 1992 in the preface to ICD-10 – is a way of seeing the world at a point in time" (1, p. vii). Thirty years on, the response to the publication of the American Psychiatric Association (APA)'s DSM-5 (2) suggests that the world of psychiatric science is in disarray.

T. Insel, writing as Director of the world's most powerful neuroscience funding institution, the USA's National Institute of Mental Health (NIMH), spelled out one of the main critiques, that DSM-based research had failed to translate into tangible improvements in patient care. In a blog introducing NIMH's alternative Research Domain Criteria (RDoC) framework, Insel indicated that "NIMH will be reorienting its research away from DSM categories" (3). The sparring parties subsequently clarified that DSM remains a helpful basis for clinical work (4). Yet, this left the world of psychiatric science still apparently at risk: a discipline lacking a unified theoretical framework, with researchers divided between NIMH and APA.

But a crisis, as psychiatry above all recognizes, is an opportunity as well as a threat, and it is with the opportunities opened up by current debates over psychiatric classification that we are concerned in this paper. Understood in their historical context, we suggest, these debates are a mark not of theoretical incoherence but rather of the particular and specific challenges of psychiatric science.

Recent commentators have addressed these challenges from a number of theoretical perspectives (see for example, 5). In this paper we take instead the long view provided by three time slices from 20th century psychiatry – one early, one middle and one late century time slice. Each time slice points a number of lessons for more effective translation of research into practice. Embraced with confidence, we conclude, these lessons could put psychiatry very much at the forefront of 21st century translational medical science.

FIRST TIME SLICE: 1913 AND JASPERS' *GENERAL PSYCHOPATHOLOGY*

Our first time slice is 1913, the year of publication of K. Jaspers' *General Psychopathology* (6). Celebrated in recent centenary events and publications (7), Jaspers wrote *General Psychopathology* at a time like our own of rapid advances in the neurosciences, psychiatry's "first biological phase", and the challenge he took up remains very much at the heart of the challenge of translation we face today.

Jaspers, a psychiatrist as well as philosopher, had worked in the neurosciences and was well aware of their potential (8). But their ambitions, he believed, had become overblown. He was concerned in particular that mental disorders demand meaningful understanding as well as the causal explanations delivered by the brain sciences (9). This was the essence of Jaspers' challenge. And it is the challenge of translation. Translation of research into practice means nothing more nor less than translating between the objective findings of the brain sciences and the meaningful life-worlds of our everyday subjective experience.

Avoiding "single message mythologies"

So, what are the lessons from 1913? First, that we should not underestimate the difficulty of the challenge. As a theoretical challenge, translating between meanings and causes takes us into the depths of that mother of all philosophical problems, the relationship between mind and brain. Philosophers have made progress on this since 1913, with many helpful insights into what would nowadays be formulated as a problem of translation between sub-personal and personal levels of functioning (10). But the problem as such remains.

Correspondingly then, with problems of this peculiarly difficult kind, we should be wary of claims to "solutions". As the American humorist H.L. Melken quipped, "there is always an easy solution to every human problem – neat, plausible and wrong!" (11). Psychiatry notoriously fluctuates between such "solutions". The history of psychiatry, as the German historian and psychiatrist P. Hoff has described, is one of repeated collapses into "single message mythologies" (12). Jaspers was concerned about the collapse of psychiatry's first biological phase into a brain-only mythology. Similar concerns, as we have noted, are not out of place today (13). Moreover, far from delivering improvements in patient care, some of the worst abuses of psychiatry have had their origins in (initially well-intentioned) single message mythologies (14).

When it comes to holding the line against future single message mythologies, RDoC, we believe, holds promise. Insel attributes the failure of translation of DSM-based research to its preoccupation with reliably identifiable symptoms (3). We return to reliability in the next section. But in Hoff's terms, reliability in DSM – if Insel is right – has become yet another single message mythology. The RDoC framework, correspondingly, has been launched with the express intention of providing an open and inclusive framework hospitable to a plurality of research paradigms (15).

Resources for a pluralistic approach

Good intentions, of course, may not be enough. But there is no lack of resources for building a pluralistic approach. The new sciences of the mind range from the cognitive and related sciences (16), with their potential for computational methods (17,18), through the social and anthropological sciences, including the proven translational potential of theories of the social construction of meaning in such core areas as dementia care (19,20), to novel applications of "naturalized" and other clinically realistic phenomenologies (21,22).

The risk, though, with all this variety in play, is that while psychiatric science may avoid the blind alley of yet another single message mythology, it becomes, as psychiatry by the end of the first half of the 20th century had become (23), factionalized and fragmented. It is to the lessons for today from mid-20th century psychiatric science that we turn next.

SECOND TIME SLICE: 1959 AND THE WHO CLASSIFICATION MEETING IN NEW YORK

Fast forward then, from Jaspers to 1959 and to a meeting on psychiatric classification convened by the World Health Organization (WHO) in New York. It is from this meeting that our current symptom-based classifications, both ICD and DSM, are ultimately derived. But the story, as standardly told, of how ICD and DSM were derived from the 1959 meeting misses a detail that is key to understanding how 21st century psychiatric science might avoid the equal and opposite traps of single message mythologies and of fragmentation. In this section we will first reprise the story of the 1959 meeting, in standard and in revised versions, and then draw out the lessons for today.

The story, as standardly told (23,24), runs essentially as follows. The WHO convened the New York meeting with the aim of achieving international consensus on psychiatric classification. This was a priority for the WHO because the then-reigning nosological chaos in psychiatry stood in the way of its attempts to establish reliable comparative epidemiological data on rates of morbidity worldwide. The meeting thus brought together a small international group of senior psychiatrists of the day to make recommendations.

A distinguished North American philosopher of science, C. Hempel, was invited to open the meeting with a keynote lecture on the nature and purpose of scientific classifications. Drawing on his work in a theory of science called logical empiricism (a form of positivism, 25), Hempel talked about how sciences progress from descriptive to theoretical stages. Psychiatric classifications, he is then standardly reported as suggesting, had become fragmented because psychiatry was attempting to produce theory-based classifications of mental disorders while still at a descriptive stage in its development as a science. The reliability (agreement in use) of psychiatric classifications could thus be improved by pulling back from theory, at least for the time being, and basing psychiatric classifications instead on descriptively defined symptoms.

The meeting, so the standard story continues, took Hempel's point; the proposal for a descriptive classification was reported to the WHO (26); a new symptom-based glossary to ICD-8 was prepared (27); the success of the glossary in improving the reliability of psychiatric classifications led to the first fully symptom-based classifications in ICD-9 (28) and DSM-III (29); and a descriptive symptom-based approach driven by the need for reliability has remained the basis of subsequent editions of both classifications up to and including DSM-5.

Much of this story is right. The key detail though, the detail that is key to the lessons from the New York meeting for psychiatry today, is that it was not the philosopher C. Hempel who suggested the move to a symptom-based classification, but one of the psychiatrists present, A. Lewis (30).

A transcript of the actual meeting (published in 31) shows that Hempel did indeed emphasize the importance of

improvements in reliability for psychiatric science. But what Hempel had in mind in his lecture was the reliability of research in the then dominant (in the USA) paradigm of psychoanalysis. It was instead Lewis who saw the potential of this approach for epidemiological psychiatry. Lewis, moreover, far from believing a symptom-based approach to be the research panacea it was to become, called for a *pluralistic* approach. For "epidemiological work" – Lewis said (with the work of the WHO specifically in mind) – we should "eschew categories based on theoretical concepts and restrict ourselves to the operational, descriptive (i.e. symptom-based) type of classification". For other purposes, he continued, including other research purposes, any classification that is "based on a theory which seems a workable, profitable one may be very appropriate" (30, p. 34).

In itself this detail from the story of the 1959 meeting says something about the need for two-way collaboration between philosophy and psychiatry (30). We return to the importance of collaboration in research below. For now, though, we want to focus on what we can learn from the revised story of the 1959 meeting, respectively for the reliability of psychiatric classifications and for their validity.

Keep reliability

Embroiled as we are now in a crisis of psychiatric classification, it is important not to lose sight of how well the original move to symptom-based classifications, with its associated improvements in reliability, was received. It seemed indeed to many at the time that psychiatry had finally come of age as a medical science and the new approach to classification through the ICD (28) as well as DSM (29) was readily taken up in many parts of the world.

Small wonder, then, with expectations running so high, that when reliability-based classifications in the event failed to deliver on their early promise, a correspondingly deep disillusionment should have set in. Insel makes this explicit in his blog: "The strength of each of the editions of DSM has been reliability… The weakness is its lack of validity" (3). Advocates of DSM, it seems, agree. In setting the "research agenda for DSM-V", D. Kupfer, M. First and D. Regier argued that the primary strength of the DSM's reliability-based descriptive approach is "its ability to improve communication among clinicians and researchers, not its established validity" (32, p. xviii). What is needed, they continued, is "an as yet unknown paradigm shift" that would "transcend the limitations of the current DSM paradigm" (32, p. xix).

Lewis, not to say Hempel, would have seen any downgrading of reliability as a shortcut back to the nosological chaos from which psychiatry had been delivered by the outcomes of the 1959 New York meeting. This is essentially because without reliably repeatable observations there is no reliably repeatable research and without reliably repeatable research there is no science. Lewis indeed, in a later publication, warned of the dangers of psychiatry retreating from the disciplines of observational science. In his foreword to ICD-9, he emphasized the need for psychiatry to remain ever vigilant in guarding "the gate of observation" (33).

A first lesson then from the 1959 meeting is that, if we want to avoid a return to fragmentation and chaos, we should build on, not down-grade, reliability. The failure of DSM-based research to deliver comes not from an overreliance on reliability as such but rather from an overreliance on reliably-defined *symptoms*. The revised Lewis-plus-Hempel version of the story of the meeting fits well with the aspirations of the RDoC. As Insel and others have emphasized (15), RDoC is not a classification. It is intended rather as a symptoms-plus-theory framework for assimilating the results of future research which, in breaking away from the symptoms-only basis of DSM, will accommodate pluralistic approaches of exactly the kind Lewis had in mind.

But add validity

The message from 1959 is thus about hanging on to reliability as the basis of observational science. But there is nothing in this message about abandoning validity. To the contrary, Lewis' interpretation of Hempel's account of the development of sciences from descriptive to theoretical stages directly anticipates Insel's and Kupfer et al's shared concern (in the above quotes) with the importance of validity.

Just what validity means in science is harder to pin down. Hempel in his 1959 lecture had a good deal to say about validity, but it was all rather technical and had little influence on subsequent developments in psychiatric classification (30). Logical empiricism itself, indeed, as Hempel's guiding theory, has since proved to be very far from the last word on the nature of science. It remains helpful as a source of insights, for example into the much misused (in psychiatry) concept of "operationalism" (25). But when it comes to validity, new insights have come rather from post-logical empiricist philosophy of science. Of particular relevance to current debates is the work of the North American philosopher of science, A. Fine, showing that even in physics there is no gold standard for validity. Criteria of validity in science are instead set locally in a "fit for purpose" approach according to what seems appropriate to those concerned (34).

With reliability, therefore, so too with validity there is a neat fit between the revised Lewis-plus-Hempel story of the 1959 meeting and today. Lewis' pluralistic vision for psychiatric science based on theories that seem to those concerned "workable and profitable" closely tracks Fine's (1999) locally set "fit for purpose" criteria of validity. With our third and final time slice, we come to what "fit for purpose" validity means specifically for translational research in 21st century psychiatry.

THIRD TIME SLICE: 1997 AND THE DALLAS CONFERENCE ON CLASSIFICATION

Organized by the North American psychiatrist and philosopher J. Sadler, the historical importance of the 1997 Dallas conference is that it brought together for the first time on a fully collaborative basis each of the principal stakeholder groups concerned with psychiatric classification, i.e. not just clinicians and researchers but also patients and carers. The Dallas conference inspired a series of similar conferences in London, hosted by the UK's Department of Health in partnership with the WHO, that in turn led to a collaborative programme on good practice in mental health assessment (35).

In this final section, we argue that closer collaboration between clinicians/researchers and patients/carers is one of the keys to "fit for purpose" validity in translational psychiatric research. This is essentially because psychiatry is distinctive as a medical science in being concerned not with the regularities of this or that sub-system of persons (as cardiologists are concerned with the cardiovascular system, for example), but rather with the diversity of what the philosopher of mind K. Wilkes called "real people" (36). We will look at how the diversity of real people is reflected in three challenges to "translational validity" presented by the concept of mental disorder: its contested meanings, the complexity of its presenting symptoms, and its value-ladenness.

Translational validity and contested concepts of mental disorder

For much of the second half of the 20th century, psychiatry was dogged by the question of just what exactly *is* mental disorder. The question as such was not new: since classical times (37), and across diverse cultures (38), mental disorder has been understood in widely different ways, ranging from the medical to the moral (or psychological). But prompted by the American psychiatrist T. Szasz's skeptical claim that mental disorder is simply a myth (39), the 1960s and 1970s witnessed an unprecedented flowering of different conceptions of mental disorder (40), and the debate between different models continues to this day.

We do not have space here to engage with the "pros and cons" of all the many different models in this debate (see 41 for a summary of main positions). One way to understand the debate as a whole, however, is as a dispute between the various "cultures" of psychiatry, the different models thus representing the different perspectives on mental disorder of the various mental health professions (medical, psychological and social) and of patients and carers. But there is the same range of perspectives involved in all areas of medicine. So understood, therefore, the operative question for translational validity becomes not "which?" but "why?", i.e., not which if any of the proposed models is right, but why the debate has been about *mental* disorder with no corresponding debate about bodily disorder.

Critics of psychiatry are inclined to answer the "why?" question in terms of difficulties of definition. But bodily disorder is at least equally difficult to define (42). For instance, are obesity and tooth loss disorders? The "why?" question, we suggest, is better answered in terms not of difficulties of definition of the concept of mental disorder, but rather of difficulties in use arising, in part but importantly, from the need for an integrated biopsychosocial approach. In single-system areas of medicine, such as cardiology, a relative focus on biological factors may at least approximate to good medicine. Something similar might be said of neurology to the extent that it too is a single-system area of medicine. But in psychiatry no such single-system approximations are available, because the real people with which psychiatry is concerned are themselves biopsychosocial in nature.

In clinical work the importance of an integrated biopsychosocial approach in which the different cultures of psychiatry come together to serve the diverse needs of patients has been recognized for some time (43). If in clinical work, therefore, why not in research? Such research will draw on the resources for a pluralistic ("mind as well as brain") approach discussed in section 1. As such, it would be informed by a variety of theories that, as Lewis (section 2) might have put it, seem "workable and profitable". So, this is not a recipe for quick wins. But such research, consistently with Fine's (section 2) locally set "fit for purpose" criteria, would have at least *prima facie* translational validity.

Translational validity and the complexity of psychiatric symptoms

But why does research of this kind require closer collaboration between researchers and patients/carers? Why does it require more than an integrated approach between researchers with expertise-by-training from within psychiatry's different professional cultures – biological, psychological and social? Such an integrated approach is difficult enough. Why then do we need to add the further challenges of closer collaboration with patients and carers?

The short answer is that patients and carers add to the expertise-by-training of professional researchers their own distinctive expertise-by-experience. There is no hard and fast divide here, of course. Many professional researchers have experience as patients and/or as carers, and many patients and carers have expertise in one or another research discipline. Correspondingly, "closer collaboration" could take place in different ways and at different levels depending on the demands of the research in question (44). In the UK, closer collaboration in all areas of health-related research has been the norm for some time, although debate continues as to its benefits (45). But that both kinds of expertise in one form or another have to be in play, if research at least in mental health is to translate successfully

into practice, is a consequence of the complexity of the very symptoms of mental disorder.

Again, a comparison between cardiology and psychiatry makes the point. Angina (heart pain) is similar from one patient to the next. In this respect, then, angina is a relatively simple symptom. But hallucinations, delusions, obsessions, depressive and other presenting symptoms of mental disorder all vary widely in both form and content between different individuals, between cultures, and at different historical periods. Added to the sheer diversity of such symptoms, furthermore, is a far greater degree of individual variation in attributed meanings: a given hallucination, for example, may be interpreted by one person medically and by another in spiritual terms (46). Hallucinations, indeed, are now well recognized to occur commonly within the normal population (47), and this is an area in which the clinical importance of bringing together expertise-by-training with expertise-by experience has been recognized for some time (48).

There is, of course, much that expertise-by-training can bring to tackling the complexity of psychiatric symptoms. Besides the standardized checklists so widely employed in contemporary psychiatric research, a range of other methods, phenomenological and empirical, qualitative and quantitative, have been and continue to be used by experts-by-training from each of the wide range of research disciplines noted towards the end of section 1 above.

But to the extent that such methods in the hands of experts-by-training alone have largely failed the test of translation, it is no less than good science to try something new. Closer collaboration is a big step, certainly. But it is a step that builds on the established and growing (good) practice of including patients and carers in research teams (45). It is for a big step, for a paradigm change, that as noted above both Insel (for RDoC, 3) and Kupfer et al (for DSM, 32) have called. There is, moreover, a growing resource for closer collaboration in clinical work and training on which to draw (see for example the UK's recently revised National Occupational Standards for Mental Health, 49). So, why not try the big step of closer collaboration in research?

Translational validity and the value-ladenness of mental disorder

The need for closer collaboration in translational research is given a particular edge by the value-ladenness of mental disorder and the way this is reflected in sometimes radically different desired outcomes of treatment. The value-ladenness of mental disorder has been subject to different theoretical interpretations within a wider debate about the meanings of concepts of disorder in general (50). Leaving aside though these theoretical considerations, a contemporary example of its practical significance in relation to outcomes is the tension between the traditional medical outcome of symptom control and a "recovery model" focussed on improving quality of life (51).

Once again, it is important to be clear that the difference in this respect between bodily and mental disorders is only a matter of degree. Yet it is a significant difference nonetheless. In bodily medicine, symptom control and quality of life normally go hand in hand (as in controlling angina). But in psychiatry the relationship is more complex. This is partly a matter of side effects: antipsychotic medications, for example, may help to control psychotic symptoms but at the expense of side effects that in some cases impair a person's quality of life by reducing his/her ability to hold down a job or maintain close personal relationships. It is though also a matter of riding rough-shod over the very different ways in which psychiatric symptoms themselves may be valued or disvalued. A given hallucination, for example, whether understood medically or spiritually, may be experienced positively by one person and negatively by another (52).

A further aspect of the value-ladenness of mental disorder is the way in which, besides their obvious negative aspects, some disorders may also have positive aspects, including in some cases enhanced cognitive skills. These positive aspects are crucial to quality of life as a desired outcome in that, if recognized and developed, they bring with them improved prospects for employment. Anxiety (53) and mood disorders (54), for example, have been linked with creativity; and people with autism are beginning to be recruited by some high-tech industries for their particular cognitive skills (55). There is compelling evidence, furthermore, suggesting that people with certain psychiatric disorders may actually be more rational in certain tasks than the non-clinical population (56). For instance, people with schizophrenia are less vulnerable to a statistically normal but irrational tendency to gamble when faced with a certain loss (57); and people with autism are more logically consistent than controls when making decisions involving possible financial gain, because they are not distracted by emotional contextual cues in the same way as controls (58,59).

There is evidence too that delusions and distorted memories, which as symptoms of psychiatric and neuropsychological disorders are often regarded as paradigmatic instances of irrationality, can play useful pragmatic and epistemic functions. Delusions may reduce anxiety and enable normal learning processes to resume and enhance memory after the prodromal phase of psychosis, by offering some explanation for hypersalient stimuli (60). Distorted memories and confabulatory narratives may help a person with impaired or declining autobiographical memory retain some sense of self with positive effects on wellbeing, mood regulation and socialization (61,62).

Once again, there is no knock-down argument in all this for closer collaboration in research. The argument though has been widely accepted in policy and practice, with growing resources for more effective ways of working collaboratively towards a diversity of desired outcomes. In the UK, for example, the National Occupational Standards noted above (49) bring together co-production with the skills for values-based practice (63) as twin resources for recovery-

oriented care. There are early moves towards closer collaboration in research in bodily medicine (64). And, further reinforcing the continuity between psychiatry and bodily medicine, values-based practice is already being extended from mental health into other areas of medical and surgical care (65). Psychiatry, then, in developing more collaborative models to meet its own particularly acute challenges of translation, would be leading the field for medicine as a whole.

CONCLUSIONS

In this paper, we have outlined lessons for the future of translational research in psychiatry from three time slices of the history of 20th century psychiatry:

- From 1913, and the publication of Jaspers' *General Psychopathology*, the lesson was that we should beware simple solutions (Hoff's "single message mythologies"), adopting instead a pluralistic approach encompassing the resources equally of the sciences of the mind (including the social sciences) and the sciences of the brain.
- From 1959, and the birth of our current symptom-based classifications in Lewis' response to Hempel's lecture on logical empiricism, the lesson was that, in pluralistic as in any other research, reliability (as the basis of observational science) is essential, but that we should add to it an understanding of validity appropriate to the challenges of translational research.
- From 1997 and the Dallas conference came the lesson that one of the keys to this "translational validity", as we called it, is closer collaboration in research bringing together the resources of expertise-by-training with those of expertise-by-experience. Such collaboration is challenging and may take different forms according to the demands of a given research question. But its *prima facie* importance is evident in the unique challenges to translation presented by the complexity of mental disorder, particularly as reflected in the diversity of desired treatment outcomes.

Taken together, these lessons – a pluralistic approach, reliability *and* validity, and closer collaboration among all relevant stakeholders – provide an emerging framework for psychiatric science that, in building on 20th century advances, points the way forward to more successful translation of research into practice.

Our chosen time slices are of course not definitive of the history of 20th century psychiatry. The lessons they offer are intended to help us look forward, not back. These lessons, moreover, as we have indicated, are not confined to psychiatry. The challenge of translation is greater in psychiatry than in other areas of medicine for the sufficient reason of its greater complexity. The brain is more complex than, say, the heart. But crucial to translation is the greater complexity of the actual *experience* of mental disorder. As we outlined in our third time slice, there are no less than three distinct ways in which experiences of mental disorder are more complex that their counterparts in such areas as cardiology. Small wonder therefore that, looking back, translation has been slow to get going in psychiatry. But equal reason, with the lessons of the past in mind, and with so many new resources to hand, to look forward with confidence towards successes to come.

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New trends in assessing the outcomes of mental health interventions

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Assessing the outcomes of interventions in mental health care is both important and challenging. The aim of this paper is to advance the field of outcomes research by proposing a taxonomy of the decisions that clinicians and researchers need to consider when evaluating outcomes. Our taxonomy has eight components, framed as decisions: Whose outcome will be considered? Which scientific stage is being investigated? What outcome domain(s) matter? What level of assessment will be used? Will clinical and/or recovery outcomes be assessed? Whose perspective will be considered? Will deficits and/or strengths be the focus? Will invariant or individualized measures be preferred? We propose a future focus on understanding what matters most to people using mental health services, and on the use of measures rated by service users as the primary approach to evaluating outcome.

Key words: Outcomes research, assessment measures, mental health services research

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Assessing the outcomes of interventions in mental health care is both important and challenging. It is important because producing significant outcomes, i.e., health gains attributable to an intervention (1), is the main goal of mental health services. Other important attributes of an intervention, such as accessibility, acceptability, efficiency and cost-effectiveness, need only to be considered where the intervention produces significant outcomes. Assessing outcomes is also challenging, because choosing methods, outcome domains and outcome measures all involve the balancing of conceptual, ethical and clinical considerations (2,3).

The aim of this paper is to propose a taxonomy of the decisions that clinicians and researchers need to consider when evaluating outcomes. Our taxonomy has eight components, each of which involves making explicit underpinning assumptions. We therefore frame these components as decisions.

DECISION 1: WHOSE OUTCOME?

It might be thought that the outcome for the patient is of primary importance, but the needs of at least three other stakeholder groups also need to be considered.

First, the patient's *informal carers* – their friends and family – often have substantially more contact with the patient than mental health staff, which may have powerful consequences. A UK study estimated that 4.8% of carers had terminated employment and 15.5% took a mean of 12.5 days off work per year as a result of their carer role (4). Carers also provide emotional and practical support that otherwise would be required from mental health services – estimated for people with schizophrenia being looked after by family as involving 5.6 hours per day (5). Informal carers will have their own perspectives on valued outcomes for the patient and for themselves (6). Evaluating the impact of their caring role on their mental and physical health may be a cost-effective element of an evaluation strategy, and carer-focussed measures are available (7-9).

Second, the *wellbeing of staff* may be considered as an outcome, for two specific reasons. The clinical rationale is that there is now robust evidence (10) that "parallel processes" exist in mental health services – the experience of staff within the system influences how they work with people using services. If services are for example to promote hope and empowerment, then staff need to experience hope and empowerment in their work role. The economic rationale is that providing mental health services is expensive, and the primary cost driver is human resources. A workforce with low morale, high sickness rates and poor performance is an inefficient investment (11). For both these reasons, monitoring outcomes such as staff wellbeing and morale might be justified.

Finally, *members of the public* largely fund mental health systems in many countries, whether directly through health insurance or indirectly through taxation. Therefore the public have a legitimate interest in the return on their investment (12). Outcomes of interest to the public might include reductions in antisocial behaviour such as aggressive begging, or of "odd" behaviour such as shouting at voices.

For the remainder of this paper, we focus on outcomes for patients.

DECISION 2: WHICH SCIENTIFIC STAGE?

Developed as an analogue of the phases of pharmacological product development, recent formulations have considered phases of complex psychosocial interventions (13), or more generally the phases of the translational medicine continuum (14), shown in Figure 1.

In this conceptualization, outcomes may vary according to the scientific stage of enquiry. At Phase 0 (scientific discovery) the key outcome may be the formulation of a new

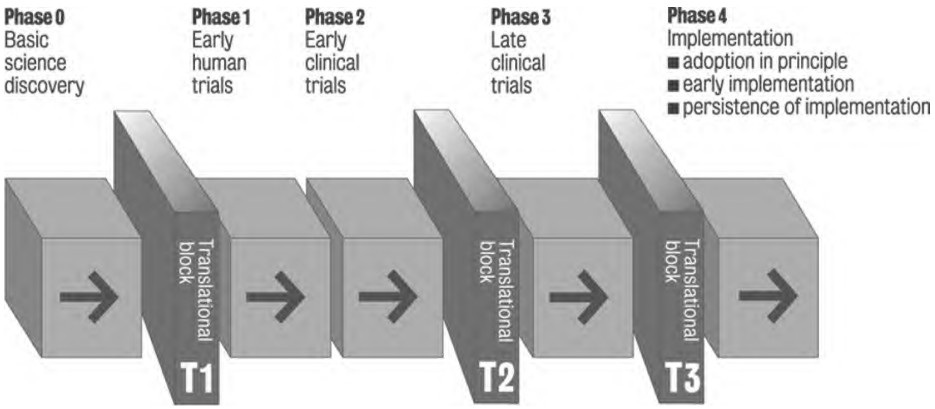

Figure 1 Phases of the translational medicine continuum

aetiological pathway or candidate risk factor for a disorder. At Phase 1 (early human trials) the key outcomes of interest are likely to be tolerability of the new intervention and dose-response. In Phase 2 (early clinical trials) the critical outcome issue is estimating the effect size of the intervention – in other words, is there an early indication that the intervention is effective, and how effective? At Phase 3 (late clinical trials) the key outcome is more specific – exactly how effective is the intervention among routine populations with the condition of interest? Finally, in Phase 4 (implementation) the outcome focus becomes more pragmatic, namely how far can Phase 2 and 3 benefits be replicated in routine clinical practice?

DECISION 3: WHAT OUTCOME DOMAIN?

An outcome domain is a conceptually distinct component of outcome. A systematic review identified seven categories of outcome domains: wellbeing, cognition/emotion, behaviour, physical health, interpersonal, societal and services (15). Choosing the outcome domain or domains to evaluate should be a separate and prior decision to choosing the outcome measure (16). In our experience, this distinction is often not maintained, with the more common starting point being identification of measures. Conflating the choice of outcome domain with choosing the outcome measure leads to three problems: inconsistency, unimportance and unfairness.

When evaluating outcome for a specific intervention, it remains common to under-specify the intended mechanisms of action and the causal pathway from intervention to outcome. This is despite the scientific consensus that evaluation should involve identification of the theory base for an intervention (13). The absence of a testable model means that the rationale for the choice of outcome domain cannot be stated, and so the choice is likely to reflect current clinical assumptions about "what matters". There has been a general movement from using service data (e.g., readmission rates) towards clinical outcomes (e.g., symptomatology) and more recently towards health-related quality of life as clinical endpoints in outcomes research. However, the result is that the evidence base remains poor for interventions targeting some important outcome domains, such as hope and empowerment (17). Explicitly identifying, with a rationale, the choice of outcome domain will increase theoretical coherence between intervention and outcome.

When evaluating whole-system interventions such as service models or when introducing outcome assessment into routine clinical settings, consideration of outcome domains is also an important first step. Mental health systems need to meet many goals, including patient benefit, harm minimization, public protection, and value-for-money. The choice of outcome domains sends a clear message about the relative balance of these goals, and hence is an influence on organizational culture. It is one means by which an organization communicates what is important, in other words its "core business".

Finally, explicitly identifying the outcome domain reduces the extent to which success is unfairly judged in relation to aspects of a patient's life which are outside the control of the mental health service. Social determinants of mental ill-health such as poverty and social inequality are well-established (18), and as services in general cannot influence wider social determinants, measures of health-related quality of life may be insufficiently sensitive. An alternative approach is to identify more proximal outcome domains, such as symptomatology or recovery support.

DECISION 4: WHAT LEVEL OF ASSESSMENT?

It is important to have clarity about the level of assessment, from the individual intra-psychic level (e.g., symptoms) through the inter-personal and immediate social environment (e.g., carers, social networks) to the broader environmental level (e.g., stigma). For example, in relation to interventions related to stigma and discrimination associated with mental illness, one can assess the outcomes of a national programme, such as the Time to Change campaign

in England (19), using whole population surveys (20), or in terms of sub-populations such as journalists (21), or in terms of the outcomes rated by individual mental health services users (22), all of which can be seen as valid and indeed complementary outcome measures.

DECISION 5: CLINICAL OR RECOVERY OUTCOMES?

Outcome assessment internationally remains primarily focussed on traditional clinical outcomes such as symptomatology, social disability and service use (e.g., admission rates). The four most commonly used measures assess social disability (Health of the Nation Outcome Scale, HONOS (23)), symptoms (Clinical Outcomes in Routine Evaluation – Outcome Measure, CORE-OM (24); Outcome Questionnaire-45, OQ-45 (25)), and needs (Camberwell Assessment of Need, CAN (26)). These are mandated for national or large regional use in Australia (27), Canada (28), England (29), Netherlands (30) and New Zealand (1). These measures have in common that they assess clinical outcomes.

Internationally there is an emerging consensus that services should be recovery-oriented (31). Recovery has been defined as "a deeply personal, unique process of changing one's attitudes, values, feelings, goals, skills, and/or roles" and "a way of living a satisfying, hopeful, and contributing life even within the limitations caused by illness" (32). International best practice is emerging (33), and it is becoming clear that organizational transformation is needed to develop a recovery orientation (34). Some dimensions of transformation include a greater emphasis on the biomedical ethical imperative of promoting autonomy (35), a changed workforce (36), a greater emphasis on patient choice, and, most relevantly, different goals of mental health care. The challenge is summarized by Repper and Perkins (37): "Traditional yardsticks of success – the alleviation of symptoms and discharge from services – are replaced by questions about whether people are able to do the things that give their lives meaning and purpose, irrespective of whether their problems continue and whether or not they continue to need help and support". The challenge is to measure recovery as an outcome in a way which is both aggregatable and meaningful.

How might this be done? A systematic review of recovery frameworks identified five key recovery processes: connectedness (social inclusion, community integration), hope and optimism, development of a positive identity, meaningfulness in life, and empowerment – the CHIME Framework (38). If the goal of a mental health system is to promote recovery, then these recovery outcomes are the appropriate domains to target. New measures are becoming available (39).

One proposal is that outcome assessment should measure valued social roles which reinforce social identity, and individual goals which contribute to personal identity (40).

Valued social roles include employee, partner, family member, friend, citizen, free (i.e. non-detained) person, etc. Their value is relatively invariant – most (but of course not all) people want a job, a relationship, contact with their family, some close friends, the ability to exercise citizenship rights such as voting, not to be held in hospital or prison, etc. Assessment tends to be quantitative and dichotomous (or at least on an ordinal scale, such as unemployed – voluntary work – part-time work – full-time work), and hence easy to aggregate with little loss of meaning. The primary advantage of these outcome measures is that they are based on normal social values, and so avoid illness-related lowering of expectations either by staff, in an effort to be realistic, or by patients with internalized stigmatizing beliefs about what they can expect in life (41). Since most valued social roles occur outside the mental health system, they orientate the actions of the service towards increasing integration and participation by the person into his/her social environment, rather than encouraging a decontextualized and service-focussed view of the person. Their primary disadvantage is their invariance – some people get along very well in life without friends, or a partner, or a job.

Individual goals differ from person to person. No standardized measure will have items such as "swim with dolphins" or any of the other idiosyncratic goals individuals set and attain on their recovery journey. Any attempt to squeeze personal identity into predefined boxes can be justifiably criticized for its loss of meaning. This does not, of course, mean that personal goals should not be included in outcome evaluation – they remain central, despite the difficulties in assessing individual goal attainment. Rather, as McNamara (42) put it, "the challenge is to make the important measurable, not the measurable important". So, an overall outcome evaluation strategy might measure two things. First, objective quality of life indicators, such as adequacy of housing, friendship, safety, employment and close relationships. Second, progress towards personal goals.

DECISION 6: WHOSE PERSPECTIVE?

Assuming that the outcome for the patient is the main focus, the question remains of whose perspective is used. Two perspectives have primarily been used to evaluate outcome.

First, and in our view most central, is the patient perspective. An emerging distinction in relation to patient-rated measures is between assessment oriented towards the experience of using mental health services and systems – patient rated experience measures (PREMs) – and assessment capturing direct health gain – patient rated outcome measures (PROMs), especially using patient-generated PROMs (PG-PROMs) (43). A range of PROMs exist, spanning both clinical and recovery outcomes (44-47). The development of PREMs is earlier stage, and has primarily focussed on satisfaction and experience of care. The main limitation of

PREMs is that they may reduce the focus on a "life beyond illness". People who use mental health services long-term can live in a "virtual institution", in which key aspects of identity (social network, sense of self, housing, etc.) are all indexed on the mental illness (48). PREMs such as satisfaction are a normative judgment influenced by the person's reference group, so in people using mental health services positive ratings may be obtained because of an atypical reference group. This vulnerability of PREMs to being rated positively because of lowered expectations means that mental health systems should as far as possible evaluate success using outcome rather than experience measures.

Second, and perhaps the traditional focus in mental health systems, is the perspective of the clinician (49-51). Staff-rated measures exist for most outcome domains. This perspective has been called the "objective" assessment and the patient rating called the "subjective" assessment, but in fact staff assessments are themselves prone to bias due for example to professional training (52), and some studies have found patient rather than staff assessments to be more reliable (53). The reality is that both staff and patient perspectives are influenced by a range of factors, and both provide useful and complementary information on outcome. The relative balance given to the two perspectives should be based on scientific, ethical, professional and pragmatic considerations.

We now consider outcome assessment from the patient's perspective.

DECISION 7: DEFICITS OR STRENGTHS?

The World Health Organization (WHO) declares that health is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (54). However, creating health-oriented rather than illness-oriented services has proved rather more difficult than the clarity of this declaration would suggest. In relation to outcome, the substantial majority of measures used in research and practice are focussed on mental illness – they assess amelioration of undesirable experiences such as symptoms or cognitive problems, reduction in risk factors such as stress, or attainment of an adequate level of functioning. Very few assess mental health, such as the use of strengths (55), the development of protective factors such as resilience, or the attainment of positive wellbeing (56).

Some argue that mental health is a distinct construct. The Complete State Model of Mental Health posits that mental health and mental illness lie on orthogonal spectrums (57). People with mental illness range from those who are "floundering" (when mental health is absent), through those experiencing moderate mental health, to those who are "struggling" (when mental health is present) as they work towards "flourishing" (high mental health, low mental illness). Epidemiological studies of adults (n=3,032) (57) and adolescents (n=1,234) (58) confirm that mental health and mental illness according to these definitions co-exist in the general population.

An alternative view is that mental health is better understood as lying on a single spectrum with positive mental health at one end and negative mental health at the other. Measures based on this approach have been developed, such as the Subjective Happiness Scale (59), which includes items such as "Compared to most of my peers, I consider myself. . .", with Likert ratings from 1 (less happy) to 7 (more happy). Some wellbeing measures include only positively worded items, which are compatible with both understandings of mental health. Examples include the WHO-5 Well-Being Index (e.g., "I have felt cheerful and in good spirits") (60) and the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS) (e.g., "I've been feeling useful") (61).

More generally, Vaillant identifies six models of mental health (62). The first model, being "above normal", relates to superior functioning in a wide range of activities, such that life's problems never get out of hand. The goal of the second model, positive psychology, is intervention to maximize positive qualities, such as self-efficacy. A recent systematic review has identified indicators of wellbeing in psychosis (63), which are now being used to inform a new intervention based on positive psychology principles (64). The third model involves maturity, shown by attainment of developmental tasks such as identity, intimacy, generativity and integrity (65). The fourth model is emotional or social intelligence, i.e., the ability to read other people's emotions. Subjective wellbeing, i.e., the experience of positive mental health, is the fifth model, and the last model is resilience, which is linked to the adaptive value of coping mechanisms.

DECISION 8: INVARIANT VERSUS INDIVIDUALIZED?

Normal practice in outcome evaluation is to use standardized measures, for which key psychometric criteria have been established as adequate. More recent attention has enlarged the focus from the usual reliability and validity concerns to also consider feasibility and clinical relevance (66). However, standardized measures have the feature of invariance – the same outcome domain is assessed for each patient. The advantage of this approach is that it allows statements about the impact of an intervention or service on a specific outcome domain, such as symptomatology. The emerging important disadvantage, however, is that the outcome domain may or may not be important to the patient.

We learn from the reports of people who use services that recovery is very individual, varying greatly from person to person (67). As well as symptomatic or functional improvement, the tipping point towards starting to develop an identity as a person in recovery can be developing a supportive relationship with a mental health worker who treated them as a person not a patient (68), or non-clinical changes such as spiritual growth (69). This variation highlights the need for caution about viewing improvement in any single domain

as universally important, and the outcome evaluation challenge of capturing individual importance using standardized assessments.

One technology that can be used to personalize evaluation is goal attainment scaling (GAS) (70). This approach involves patients prospectively identifying a personally-important goal and associated progress indicators on a typically five-point scale, using these indicators to assess progress at outcome evaluation, and then standardizing the results to allow aggregation. GAS has been used to identify and then evaluate a valued outcome in randomized controlled trials, primarily in rehabilitation medicine (71) and with older adults (72). Two systematic reviews have investigated this use of GAS. In relation to pharmacy practice, the conclusion was that GAS demonstrated high reliability, variable validity, excellent responsiveness, and was a useful methodology for evaluating effectiveness (73). In relation to physical rehabilitation, GAS was described as a sound measure, with reliability and sensitivity needing further investigation (74). Concern has been raised about sensitivity to subtle changes, responsiveness, inter-rater reliability, validity (content and construct), scaling non-linearity and lack of uni-dimensionality (75). For example, agreement on progress between a patient's therapist and an independent assessor is low (76). To these concerns, we would add that administration burden can be high, and that the GAS score (77) is not intuitive to interpret.

A new approach to address some of these issues is called the Personal Primary Outcome (PPO) list. Designed for use in randomized controlled trials and other evaluations, the PPO list comprises several outcome domains, each of which is (invisibly) linked to a relevant standardized outcome measure. At baseline, the patient chooses the outcome domain that is most closely linked to his/her goal in using mental health services, and then he/she completes the associated measure. The measure is re-administered at follow-up. The PPO list approach is currently being evaluated as a methodology for trials (78).

A second approach is to develop a standardized measure where items are selected according to patient preference. An example is the INSPIRE measure (downloadable at www.researchintorecovery.com/inspire) of recovery support, where for each item about support from a mental health worker, respondents are first asked if the item matters to them, and only if it does are they asked to rate support from the worker (47). The INSPIRE score therefore reflects the respondent's preferences, yet produces a quantitative score which can be used for monitoring change over time or can be aggregated with the scores of others.

CONCLUSION: WHAT OUTCOMES REALLY MATTER FOR SERVICE USERS?

Perhaps the most important insight developed in the last decade is that it is the point of view of the patient or service user that is the most important in deciding which outcomes to assess, and in making the actual outcome ratings. We know, for example, that quality of life is not closely related to users' needs as rated by staff of mental health services, but is closely associated with unmet needs as rated by service users (79,80). It follows that the emerging literature reporting service user views on measures (44,81) and developing new measures (82) is of paramount importance. New measures, such as the Recovery Star (83), can be independently evaluated (84) and incorporated into clinical practice (85). An additional advantage of making service user rated outcomes a principal focus is that it side-steps the issue that has bedevilled services in recent years, namely how to incentivize staff to make frequent, complete and valid outcome ratings on a long-term sustainable basis.

If we were unwisely to try to predict the central issues in mental health outcome measurement over the next decade, then we propose a relentless attention to the detail of what matters most to service users, as rated by service users.

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Impulse control disorders and "behavioural addictions" in the ICD-11

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Psychiatric classifications have traditionally recognized a number of conditions as representing impulse control disorders. These have included pathological gambling, intermittent explosive disorder, kleptomania, pyromania, and trichotillomania.

In 1992, the World Health Organization (WHO) described habit and impulse disorders (F63) as characterized by repeated acts that have no clear rational motivation, generally harm the person's own interests and those of other people, and are associated with impulses the person experiences as uncontrollable (1). In DSM-IV-TR, the American Psychiatric Association further characterized these impulse control disorders as being preceded by a rise in tension before the behaviour or when resisting the behaviour, and followed by pleasure, gratification, or relief of tension (2).

In the past two decades, the public health importance of these disorders has become increasingly apparent. For example, pathological gambling and intermittent explosive disorder are prevalent conditions (lifetime prevalence rates of 1% and 3%, respectively) that are recognized to represent a substantial burden of disease (for example, increased health concerns, family discord, and financial problems) (3,4). Furthermore, there is a growing literature addressing the psychobiology and management of all of these impulse control disorders (5-7).

Some animal models and clinical imaging studies suggest that these conditions represent "behavioural addictions", characterized by abnormalities in reward processing (8-11). As a result, proposals have been made to include compulsive sex, compulsive buying, and compulsive Internet use under this rubric, on the grounds that they too represent a large burden of disease and deserve appropriate diagnosis and treatment (7,12-14).

The WHO's development of the ICD-11 provides an important opportunity to optimize the classification and description of impulse control disorders and to address some of the controversies surrounding these putative "behavioural addictions". The WHO has emphasized that ICD-11 should pay particular attention to issues of clinical utility, global applicability, and scientific validity (15).

The ICD-11 Working Group on Obsessive-Compulsive and Related Disorders was asked to review the scientific and other information about use, clinical utility, and experience with relevant ICD-10 diagnoses, including impulse control disorders; to review the approach of the DSM-5 to these conditions, with a focus on whether this approach might be suitable and useful for global applications; and to develop proposals for ICD-11, with a particular emphasis on improving clinical utility in a broad range of settings.

The Working Group has recommended that a grouping of impulse control disorders be retained in ICD-11. These disorders should be defined by the repeated failure to resist an impulse, drive, or urge to perform an act that is rewarding to the person (at least in the short-term), despite longer-term harm either to the individual or others. Impulse control disorders would therefore include pathological gambling, intermittent explosive disorder, kleptomania, and pyromania, as well as compulsive sexual behaviour disorder.

In the ICD-10, many of these behaviours are already conceptualized in this manner under the grouping of habit and impulse disorders. Trichotillomania is also listed under the same heading, but the Working Group has recommended it to be moved to the grouping of obsessive-compulsive and related disorders in ICD-11, and that skin picking (excoriation) disorder also be added to the same grouping. Compulsive sexual behaviour disorder will be new to this grouping, and would replace the ICD-10 category of excessive sexual drive. Other putative impulse control disorders such as problematic Internet use and compulsive buying do not appear at this time to have enough data to support their inclusion as independent mental health conditions.

A first key controversy in the field is whether pathological gambling and related conditions should be characterized as "behavioural addictions" and thereby be subsumed under a larger category that is more closely related to substance-related disorders. While a good deal of literature supports the idea that individuals with pathological gambling have altered reward circuitry (6), they also have other brain abnormalities. For example, prefrontal cortical dysfunction appears similar between gamblers and individuals with

mania (16,17). Additionally, although there is a shared genetic vulnerability between gambling and alcohol addiction, pathological gambling also shares genetic vulnerability factors with major depressive disorder (18). Therefore, categorizing gambling behaviour as an addiction, although heuristically appealing, seems premature based on the evidence. Furthermore, the change in categorization does not have clear clinical utility, insofar as a range of treatment approaches, other than those used in the treatment of substance addictions, may be useful for pathological gambling (for example, lithium and exposure therapies) (19,20).

A second key controversy in the field is whether compulsive sexual behaviour disorder should be included in the nosology. On the one hand, it is important that the classification does not pathologize normal behaviour. On the other, it is desirable that the classification allows for appropriate diagnosis and treatment of disorders that impact public health (21). Based on the definition of impulse control disorders as characterized by the inability to control behaviour despite its negative consequences, the Working Group recommended that compulsive sexual behaviour disorder be included in that grouping.

A third key controversy in the field is whether problematic Internet use is an independent disorder. The Working Group noted that this is a heterogeneous condition, and that use of the Internet may in fact constitute a delivery system for various forms of impulse control dysfunction (e.g., pathological game playing or pornography viewing). Importantly, the descriptions of pathological gambling and of compulsive sexual behaviour disorder should note that such behaviours are increasingly seen using Internet forums, either in addition to more traditional settings, or exclusively (22,23). The DSM-5 has included Internet gaming disorder in the section "Conditions for further study". Although potentially an important behaviour to understand, and one certainly with a high profile in some countries (12), it is questionable whether there is enough scientific evidence at this time to justify its inclusion as a disorder. Based on the limited current data, it would therefore seem premature to include it in the ICD-11.

A fourth key controversy is how best to draw thresholds for these disorders so that inappropriate diagnoses are not rendered for behaviours that are either normative (for example, sex) or simply illegal (for example, stealing). The WHO has emphasized a distinction between symptoms and disability (24). Where there is a continuum between normal and pathological behaviour, associated impairment may become a key determinant of whether or not a behaviour is disordered. An additional important consideration, from a public health perspective, is whether efficacious treatments are available. As noted above, these have now been developed for all impulse control disorders, particularly pathological gambling and intermittent explosive disorder (25,26).

There are a number of important differences between the proposals for the ICD-11 and the approach taken in the DSM-5. These stem in part from the WHO's emphasis on clinical utility in a broad range of settings. In the DSM-5, the impulse control disorders grouping was dismantled, and pathological gambling was moved to the same section as substance addictions. Although evidence may indicate that pathological gambling resembles substance addictions in many ways, data also support its relationship to other impulse control disorders such as kleptomania, intermittent explosive disorder, and compulsive sexual behaviour (14). The outward clinical similarities of these disorders (that all of these behaviours are rewarding, at least initially, that they lead to feeling out of control, that the person reports urges or cravings, that no substance is taken into the body, and that there are no indications or outward signs of intoxication) further supports their unique categorization as impulse control disorders.

Another difference between the proposals for ICD-11 and DSM-5 is that the DSM-5 rejected its own Sexual and Gender Identity Disorders Work Group's proposal to include "hypersexuality". One objection to this proposal was its implicit normative reference to the "right amount" of sexuality. The ICD-11 Working Group believes that it is more clinically useful – both in terms of conceptualizing the symptomatology and of treatment strategies – to view compulsive sexual behaviour disorder as being related to other disorders that are also characterized by repeated failures to resist impulses, drives, or urges despite longer-term harm. Therefore, the Working Group has proposed replacing the ICD-10 concept of excessive sexual drive with a term that places greater emphasis on behaviour, and moving this condition to the grouping of impulse control disorders rather than placing the primary focus on the fact that the behaviour involved is sexual in nature.

The ICD-11 will be used globally, in a broad range of specialist and primary care settings, often by non-specialized health workers. There has been growing emphasis on encouraging screening for substance use disorders in these settings, and one advantage of expanding the substance use category to include behavioural addictions would be the encouragement of similar assessment and treatment approaches for a range of conditions, which taken together do constitute a major health problem but are often neglected by individual practitioners as well as by health care systems. At the same time, however, much remains unknown about the underlying psychobiology and optimal management of these conditions, some of them have only been described in Western contexts, and the boundaries between disorder and normality remain contested.

The Working Group therefore recommends, based on the current evidence, that there be a category of impulse control disorders and that it include pathological gambling, kleptomania, pyromania, compulsive sexual disorder, and intermittent explosive disorder. This approach differs from DSM-5, which splits these disorders across diagnostic categories. Instead, the ICD-11 proposal recommends keeping these together, so that clinicians can screen for them all. We

believe that this approach is much simpler, will be easier for clinicians to use, is more continuous with the previous classification, and will be more feasible in low-resource settings than the DSM-5 approach.

All proposals for the ICD-11 will be made publically available for review and comment. These recommendations therefore represent only a starting point, and set the stage for a global exchange about how best to address the nosology of these behaviours with the goal of improving its clinical utility. In addition, the proposals for ICD-11 will be field tested using two main approaches: an Internet-based approach and a clinical settings (clinic-based) approach.

Internet-based field studies will be implemented primarily through the Global Clinical Practice Network, a network currently consisting of nearly 10,000 individual mental health and primary care professionals in more than 100 countries (www.globalclinicalpractice.net). Clinic-based studies will be implemented through the network of collaborating international field study centers appointed by the WHO. The timing of the review and comment processes and of field studies will be such that their results can be integrated into the ICD-11 prior to it submission to the World Health Assembly for approval.

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Suicidal behavior disorder as a diagnostic entity in the DSM-5 classification system: advantages outweigh limitations

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Suicidal behavior takes over a million lives worldwide every year. Non-fatal suicidal behavior is estimated to be 25 to 50 times more common (1). Finding ways to identify those at risk is a key public health goal, but researchers and clinicians alike have been stumped in the quest to decrease suicide rates using primary, secondary and tertiary prevention strategies. Our predictors simply do not work well, especially in identifying short-term risk.

One potential contributor to the poor performance of predictors may relate to how well they are identified and tracked in medical records. We have proposed a remedy for an essential risk factor for both suicide attempt and suicide: a prior history of suicidal behavior. Defining suicidal behavior disorder as a separate diagnosis (2) and providing clearly delineated criteria would bring suicidal behavior in line with parameters established by the WPA, promoting common, cross-national nomenclature and language for psychiatric disorders. Importantly, it would lead to methods to identify suicidal behavior in individual patients, with prominent documentation in medical records, key to secondary and tertiary prevention strategies.

WHY SHOULD SUICIDAL BEHAVIOR BE A SEPARATE DIAGNOSIS?

Although suicidal behavior often occurs in the context of psychiatric conditions, this is not invariably the case. For example, in the US, about 10% of people who die by suicide have no identifiable mental disorder. In China, estimates rise to 37% (3). On the other hand, even among the psychiatric conditions associated with high risk for suicidal behavior, most patients do not engage in it. For example, studies of the general population reveal that, among those who meet criteria for bipolar disorder, 29% report a lifetime history of suicide attempt (4). This means that the vast majority does not have such behavior. Thus, suicidal behavior does not appear to be an intrinsic dimension of any particular psychiatric disorder.

Considering suicidal behavior a comorbid condition is more apt and comports well with what is known about its epidemiology, which shows that it co-occurs with a vast array of psychiatric conditions. However, in direct contrast to this observation, our current nosology includes suicidal ideation and suicide attempts as a symptom of either major depressive episodes or borderline personality disorder. This implies that suicidal behavior is not as central a concern in schizophrenia, alcohol use disorder or post-traumatic stress disorder. Yet all of these disorders are associated with significant risk for suicide attempt or death.

Defining suicidal behavior as a separate diagnosis can make approaches to its identification better integrated into clinical practice

Patient examinations start with an ascertainment of the presenting problem. From there, the clinician fleshes out the current diagnosis, conducts an overview of symptoms to determine whether additional comorbid conditions are present, and undertakes a mental status examination focused on the current mental state. If there is no evidence for depression or borderline personality disorder and the patient does not report suicidal ideation or behavior during the mental status examination, there is no natural place for the clinician to be primed to identify past suicidal behavior.

The fact that suicidal ideation waxes and wanes over time sets up a perilous situation in which key information may be missed. Moreover, even in cases when the past suicide attempt is identified, data about suicide risk is often lost during hand-offs and is not included in discharge summaries (5). Hospitals or clinics with robust methods for documentation of suicide risk may be able to structure medical records so that this data is always recorded, but in less structured environments, the risk of non-identification is significant.

Suicidal behavior meets validity and reliability criteria as well as other psychiatric conditions

Interestingly, suicidal behavior meets the criteria for diagnostic validity set forth by Robins and Guze in 1970 (6). It is clinically well-described, associated with biological markers, amenable to a strict differential diagnosis, confirmed in follow-up studies to occur at higher rates in those with a past

diagnosis, and familial. In a white paper identifying characteristics of diagnoses to be included in DSM-5, it was suggested that proposed diagnoses should be: a) a behavioral or psychological syndrome or pattern that occurs in an individual; b) associated with clinically significant distress or disability; c) diagnostically valid (e.g., have prognostic significance, respond to treatment); d) clinically useful (e.g., enhance assessment and treatment); and e) reflective of an underlying psychobiological disturbance. Yet, diagnoses should not simply be culturally sanctioned responses or reflect solely social deviance or conflicts with society. In addition, three types of validators have to be present (7): antecedent validators, concurrent validators and predictive validators. Suicidal behavior meets all of these criteria.

As to antecedent validators, the presence of a psychiatric condition is certainly the most recognized risk factor for suicidal behavior. However, environmental risk factors such as unemployment, marital disruptions and financial crises are also clearly linked to risk. From familial and twin studies, suicidal behavior is known to aggregate in families, independent of the transmission of mood or other psychiatric disorders (8). Of note, there are also well-known variations in suicide and suicide attempt rates depending on sociodemographic (sex, age) and cultural factors (ethnicity, country of origin, religion). Thus, the four major categories of antecedent validators are present in suicidal behavior.

In terms of concurrent validators, there is ample evidence for the presence of concomitant features that are unrelated to diagnostic criteria, but signal risk for suicidal behavior. Examples include features from cognitive (problem solving difficulties, cognitive rigidity), emotional (hopelessness, agitation, depressed mood), temperament (aggression, impulsivity), and personality (borderline, narcissistic or antisocial personality disorders) domains. There are also several biological markers associated with risk, such as the central nervous system serotonergic hypofunction and impaired negative feedback of the hypothalamic-pituitary-adrenal axis frequently observed in both attempters and those who die by suicide. Importantly, suicidal behavior is comorbid with many diagnoses, ranging from schizophrenia to alcohol use disorders to mood disorders. However, other disorders, such as Cluster A and C personality disorders, appear to convey less risk.

Three categories of predictive validators exist and one is easily met by suicidal behavior: diagnostic stability. Perhaps the most clearly documented predictor of future suicidal behavior is a history of suicide attempt. However, like many psychiatric conditions, course of illness is highly variable. Some individuals only make one suicide attempt in their life, whereas others may go on to make many attempts or to die by suicide. As far as treatment response is concerned, suicidal behavior is similar to other conditions wherein several treatments are of utility, such as clozapine for suicidal behavior in schizophrenia or cognitive therapy, but not all individuals respond.

Another key factor in determining the eligibility of a disorder for inclusion in DSM-5 was evidence for reliability and validity of the definition. The definition of suicidal behavior in DSM-5 Section III is based on the one proposed by O'Carroll et al in 1996 (9), endorsed by the Institute of Medicine in 2002. It is consistent with the US Centers for Disease Control definition and the Food and Drug Administration definition, both based on the Columbia Classification Algorithm for Suicide Attempts (C-CASA) (10). Data from a number of sources document that this definition is reliable. For example, data collected by Columbia Suicide History Form shows an inter-rater reliability coefficient of 0.97. This same definition is used by the Columbia-Suicide Severity Rating Scale (C-SSRS) (11), which has excellent validity when compared to determinations made by an expert evaluation board (>95% sensitivity and >95% specificity for suicide attempts).

LIMITATIONS

Several objections to suicidal behavior as a diagnosis have been raised. Critics are concerned that suicidal behavior is a symptom. However, other diagnoses such as enuresis or pyromania are also included in DSM-5, although they are arguably less complex than suicidal behavior. In particular, suicidal behavior has several dimensions based on the degree of intent to die, the level of detail employed in planning, or the violence of the method.

Another criticism is that considering suicidal behavior as a diagnosis may lead to the "medicalization" of behaviors such as homicide. However, while the vast majority of suicides are associated with psychiatric conditions, only 34% of homicides are (12). Moreover, suicidal behavior is already a focus for physicians and other clinicians and clearly in the medical domain. Of course, homicide and assault can be expressions of psychopathology, for example in the context of psychosis (12), but this appears to be so in a minority of cases.

Finally, concerns that inclusion of suicidal behavior in DSM-5 may increase liability for psychiatrists have been raised. However, at least in the US, patient suicide has been a leading factor in lawsuits against psychiatrists for decades. Instead of increasing liability, embracing suicidal behavior as a distinct disorder may enhance our ability to communicate during hand-offs and to maintain focus on it as a significant clinical concern.

Critically, its inclusion may enhance research based on medical records and large insurance or national databases, which are some of the few resources where a large enough base population to generate enough suicides exist, and can provide opportunities to uncover novel predictors of risk.

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Social neuroscience and its potential contribution to psychiatry

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Most mental disorders involve disruptions of normal social behavior. Social neuroscience is an interdisciplinary field devoted to understanding the biological systems underlying social processes and behavior, and the influence of the social environment on biological processes, health and well-being. Research in this field has grown dramatically in recent years. Active areas of research include brain imaging studies in normal children and adults, animal models of social behavior, studies of stroke patients, imaging studies of psychiatric patients, and research on social determinants of peripheral neural, neuroendocrine and immunological processes. Although research in these areas is proceeding along largely independent trajectories, there is increasing evidence for connections across these trajectories. We focus here on the progress and potential of social neuroscience in psychiatry, including illustrative evidence for a rapid growth of neuroimaging and genetic studies of mental disorders. We also argue that neuroimaging and genetic research focused on specific component processes underlying social living is needed.

Key words: Social neuroscience, psychiatry, neurobiological processes, genetics, brain imaging

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The human brain has evolved to attend to, think about, and interact with other people, and we receive immense practice in these processes starting very early in life (1,2). It is therefore easy to underestimate the complexity of the component processes that underlie social living.

As Dunbar (3) has noted, the complexities of deducing better ways to find food, avoid perils, and navigate territories are trivial compared to the complexities of social living. The component processes for social living include: detecting significant stimuli in the environment and differentiating between those that are hospitable vs. hostile; differentiating among objects, nonhuman agents, and other (thinking) individuals; inferring the thoughts, intentions and emotions of other individuals, especially as it pertains to the causes of their behavior; recognizing these individuals despite changes in appearance and roles across situations, events and time; organizing these observations and inferences to provide a coherent, predictive model of others to permit the formation of stable relationships; forming stable attachments or bonds with others, including the ability to confer provisions or benefits to another based on a concern for the other's welfare; anticipating and coordinating efforts between two or more individuals; learning by social observation; recognizing the shifting status of friends and foes; using language to communicate, reason, teach and deceive others; orchestrating relationships, ranging from pair bonds and families to friends, bands and coalitions; navigating complex social hierarchies, social norms and cultural mandates; subjugating self-interests to the interests of the pair bond or social group in exchange for the possibility of long-term benefits; recruiting support to sanction individuals who violate group norms; and doing all this across time frames that stretch from the distant past to multiple possible futures (4,5).

Deficits in any one of these component processes can result in personal difficulties and interpersonal problems, that are prominent features in a variety of mental disorders (6,7). Both Axis I and II disorders are characterized by a range of cognitive deficits that negatively impact social interactions and/or by specific deficits in social cognition. For instance, autism spectrum disorders include difficulties in social perception, social motivation and/or theory of mind, which results in major impairments in social interactions. Schizophrenia and related personality disorders such as schizotypal disorder include problems in organizing social observations and inferences to develop the coherent, predictive model of others needed to anticipate and coordinate efforts between two or more individuals. Antisocial personality disorder is characterized by an inability to confer a provision or benefit to another based on a concern for the other's welfare, and a lack of empathy, which makes it difficult to form stable, healthy bonds with others. Hypoactive sexual desire disorder includes the absence or persistent deficiency of desire for sexual activity that causes marked distress or interpersonal difficulty. Several mental disorders, including borderline personality disorder, are marked by unstable relationships and moods, and impulsive behavior such as lashing out in anger. And a deficit of impulse control when interacting with others is a component in a variety of mental disorders.

Social neuroscience is a conceptual perspective focused on the specific delineation of the neural, hormonal, cellular, molecular and genetic mechanisms underlying social structures and processes. As such, social neuroscience offers a valuable perspective

for understanding important domains of mental disorders (7-12).

THE CHALLENGES OF SOCIAL NEUROSCIENCE IN PSYCHIATRY

The determination of how the human brain works and what to do when disorders develop is one of the grand challenges in science and medicine. Although the human brain shares many design features with those of other organisms, there is no doubt that it also has many unique features. The human brain contemplates the history of the earth, the reach of the universe, the origin of its species, the genetic blueprint of life, and the physical basis of its own unique mental existence. Nevertheless, animal models of mental disorders provide invaluable information about underlying mechanisms, because experiments can be performed in animals that are not possible in humans. The development of animal models is completely reliant upon knowledge gained from patient studies, which identify phenomena to be modeled. Furthermore, highly relevant animal models also exist that are used to study aspects of normal behavior, rather than pathology. These models can be integrated with patient studies and studies of healthy individuals.

To investigate the mutual influence of the biological and social environments and the mechanisms through which these influences operate, social neuroscientists, ranging from physicists to psychologists, epidemiologists to psychiatrists, philosophers to neurobiologists, and entomologists to zoologists, have begun to work together in interdisciplinary scientific teams using animal models, patient studies, and research on healthy individuals. These interdisciplinary collaborations have capitalized on a variety of methods and techniques, ranging from behavioral studies of implicit processes in lesion and split-brain patients to volumetric and neuroimaging studies across scales of neural organization in chimpanzees or healthy humans, to cellular and molecular techniques in genetics and epigenetics. Even well-traveled techniques, such as meta-analyses and electroencephalography, have seen upgrades that, for instance, permit investigations of the source and chronoarchitecture of the neural substrates of social processes (13-16). Importantly, the development of experimental manipulations of neural processes in humans through, for instance, the use of pharmacology or transcranial magnetic stimulation has also helped determine the causal significance of specific neural regions in social cognition, emotion and behavior. Finally, increases in computational speed and novel approaches for the analysis of extremely large datasets are creating opportunities to address questions across multiple levels of organization.

The potential for advances in our understanding of mental disorders in their various forms is heightened by an integration of information from multiple levels of scientific inquiry, from the social to the behavioral to the molecular and genetic levels (9). Mapping across systems and levels (from genome to social groups and cultures) requires basic, applied and clinical studies; interdisciplinary expertise; comparative as well as patient studies; innovative methods and integrative conceptual analysis. Multilevel analyses of psychopathology require a range of expertise that is not likely to be found in solitary investigators.

One can distinguish multidisciplinary from interdisciplinary approaches in this regard. While multidisciplinary research is characterized by the aggregation of expertise, interdisciplinary research is defined by synergies among experts that can transform both science and scientists. Interdisciplinary scientific research is riskier than multidisciplinary research, since it is a group product rather than the simple sum of its individual products. Accordingly, interdisciplinary teams are more subject to failure than solitary and multidisciplinary scientific efforts. But with this higher risk also comes a potential for higher payoffs. When interdisciplinary teams working on mental disorders succeed, they have the potential to produce significant scientific innovations, make progress in solving what were thought to be intractable problems, and develop more effective diagnostic procedures and treatments.

Social neuroscience facilitates such interdisciplinary development as well as allows an increase in communication and collaborations among scientists and physicians. For the past 20 years, social neuroscience has experienced a dramatic rise in the number of studies investigating mental illness which involve social behavioral disturbances. In the following section, we provide some examples of this research. The scope of social neuroscience and its relevance to psychiatry goes well beyond these examples, however. For instance, important advances have also been made showing: a) how gene regulation changes complex cognitive functions, including learning and memory, and then causes several developmental and mental disorders effecting language and social functioning (17,18); b) a role for epigenetic mechanisms in long-term memory formation (19,20), and c) the effects of early social stress on gene regulation and the epigenome, which then leads to long-lasting changes in behavior, cognition, mood and neuroendocrine responses predisposing to or sheltering from stress-related diseases later in life (21-23).

An example of the impact of social stress on gene regulation is provided by population-based research on older adults, reporting that perceived social isolation (loneliness), a chronic social stressor, is associated with the differential expression of pro-inflammatory and antiviral genes (a pattern known as the conserved transcriptional response to adversity) (24-26). The altered gene expression profiles in plasmacytoid dendritic cells and monocytes appear to be the key cellular mediators of the human immune system's transcriptional response to chronic loneliness. These two myeloid lineage antigen-presenting cells contributed disproportionately to the set of transcripts differentially expressed in the circulating leukocytes of chronically lonely individuals, whereas genes expressed by other cell types showed little differential expression as a function of loneliness. Consistent with the hypothesis that central

nervous system-mediated differences in neural or endocrine signaling are responsible for such effects, differential expression of monocyte- and dendritic cell-derived transcripts was strongly associated with the subjective experience of social isolation but showed no significant relationship to objective social network size (24).

Analyses also showed that the observed differences of gene expression profiles in antigen-presenting cells do not stem from differences in the prevalence of those cell types within the circulating leukocyte pool, but instead reflect per-cell changes in the expression of inducible genes that are flexibly transcribed depending upon environmental conditions. Thus, among all the cell types within the circulating leukocyte pool, plasmacytoid dendritic cells and monocytes appear to show a unique degree of transcriptional sensitivity to the experienced social environment.

Recent molecular mechanistic analyses have confirmed that experimental induction of social threat in a mouse model (comparable in key respects to the sense of social threat experienced by lonely humans (27)) causally increases bone marrow production of an immature, highly pro-inflammatory subtype of monocyte (28). Pharmacologic and biochemical analyses of glucocorticoid transcriptional control in the mouse model have identified a key role for sympathetic nervous system signaling in driving the hematopoietic production of glucocorticoid insensitive monocytes through a beta-adrenergic receptor-mediated pathway involving the myelopoietic growth factor GM-CSF (28).

Loneliness has been shown to increase a person's susceptibility to depressive symptomatology (29,30) and is associated with a variety of mental disorders (31). Therefore, future molecular studies focusing on gene expression or other putative functional intermediates have the potential to shed new light on the underlying mechanisms by which loneliness influences susceptibility to mental disease.

THREE ILLUSTRATIVE MENTAL DISORDERS

Recent neuroimaging research in social neuroscience has examined how the functioning of neural circuits in patients differs from that of controls. Rigorous analyses of social behaviors and disorders have identified component processes that may serve as a landmark for better understanding aspects of these disorders. We provide here a brief review of recent work on the neural underpinnings of social behavioral disturbances associated with three mental disorders.

Major depressive disorder

Major depression is a mental disorder with an estimated lifetime prevalence rate of 15-17% (32). Theories of depression point to a disruption of interpersonal processes (33) as well as of neural systems involved in socio-emotional processes (34). Individuals suffering from depression, as well as those at risk for depression, evidence a range of social deficits and appear to generate their own stressful social interactions (35-37).

The development of the concept of major depression (38), the experimental study of major depression in animals, and neuroimaging studies in humans have shed new light on how neural systems may be involved in this condition (34,39,40). For instance, with the introduction of functional neuroimaging techniques – such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) – various candidate brain areas/networks for major depression have been proposed (41-43).

A number of studies have examined the neural correlates of abnormal emotion regulation processes, which are a core feature of the disorder (44-50). Because neuroimaging studies generally include a small sample size (e.g., ranging from 9 to 44), many of these neuroimaging studies lack sufficient statistical power (43). Low statistical power reduces chances of detecting true effect (51). It is, therefore, important to keep in mind that the meta-analytic approach to functional imaging studies of major depression often provides a more accurate picture (43).

From the ensemble of these neuroimaging investigations and meta-analytic studies, a cortico-limbic model of major depression has become to emerge (41-43,52-55), postulating a dysfunction of seven key areas (lateral, medial and orbital parts of the prefrontal cortex; the subgenual and rostral parts of the anterior cingulate cortex, the hippocampus and the anterior thalamus) within and beyond the limbic system. Interestingly, this cortico-limbic model of major depression not only suggests a hyperactivity of the limbic system but also a dysregulation of the prefrontal cortex (56).

This model fits with another one proposed by Phillips et al (47,48,57) for emotion regulation, identifying two main parallel systems: a) a ventral system (including the amygdala, insula, ventral striatum, ventral anterior cingulate gyrus, ventromedial prefrontal cortex and medial orbitofrontal cortex), which is important for the bottom-up, automatic emotional evaluation of salient stimuli and the generation of emotional states; and b) a dorsal system (e.g., dorsal anterior cingulate gyrus; dorsal prefrontal cortex), which is assumed to play a crucial top-down cognitive role in the voluntary regulation of these emotional states (47,48).

A recent review including 40 fMRI studies and one PET study (44) reinforced (and specified) the role of the cortico-limbic model in major depression by dissecting it with respect to six emotion regulation subprocesses: automatic behavioral control, voluntary behavioral control, automatic attentional control, voluntary attentional control, automatic cognitive control, and voluntary cognitive control. In brief, the review showed that major depression is associated with abnormal hypoactivation of lateral prefrontal cortices, especially during voluntary control of emotional experiences, while automatic emotion regulation is achieved by activation of other brain areas, such as the medial prefrontal regions, including

the rostral and dorsal anterior cingulate gyrus (44).

These neuroimaging results suggest that depression is associated with dysfunctions in specific brain regions involved in emotion regulation, impulse control and affective responding, with social variables playing a role both as a contributing factor and as a consequence of the altered affective processing and executive functioning.

Because of the high heritability of depressive symptoms (58-60), many investigators have examined the role of genetic factors. Several studies have focused on putatively functional polymorphisms, but only a few of these genes have been confirmed in subsequent studies and meta-analyses (61). Pezawas et al (62), for instance, found that subjects with the short allele of a functional promotor polymorphism of the serotonin transporter gene (5-HTTLPR) had a decreased volume of both the amygdala and the subgenual prefrontal cortex, and showed a functional uncoupling of the subgenual–amygdala circuitry. Individuals with this allele had increased anxiety-related temperament traits, increased amygdala reactivity, and an elevated risk of depression. A large meta-analysis supported the interaction of the short allele of 5-HTTLPR and stressors in the etiology of depression (63).

Although genome-wide association studies (64) have identified interesting regions and potential new candidate genes for various mental disorders, early studies were sometimes difficult to replicate (65). Both technical improvements and larger sample sizes have produced more consistent results for major depression, but it is clear that even larger samples and meta-analyses of multiple data sets are required (66,67). The study of intermediate phenotypes provides a valuable approach: these are heritable characteristics that co-segregate with a disorder but are not a direct consequence of the disorder and can be quantified in both affected and unaffected individuals. It has been suggested that intermediate phenotypes may be influenced by a smaller number of genes as compared to mental disorder, simplifying gene discovery. Component social processes that differentiate depressed and non-depressed patients, such as perceived isolation – which has been shown to be about 50% heritable (68,69) – represent a potentially fruitful class of intermediate phenotypes.

The identification of neurobiological markers of depression may help psychiatrists target specific neural processes and regions and to personalize antidepressant treatments. However, when the depression is triggered by a repeatable environmental event (e.g., stressful life circumstances or relationship problems (29,70)), the exclusive reliance on a pharmacologic treatment may leave the patient at risk for relapse. A personalized suite of treatments informed by the field of social neuroscience can significantly improve outcomes.

Antisocial personality and psychopathy

Antisocial personality disorder is marked by a range of social aberrations involving indifference to and violation of the rights of others. The related but more narrowly defined concept of psychopathy focuses on social (e.g., untruthfulness, superficial charm, unresponsiveness in interpersonal relations) and socio-emotional features (e.g., deficits in social emotions such as remorse or shame, incapacity for love, shallow affect) (71,72).

During the past decade, a growing number of neuroimaging studies have investigated the neural substrates of antisocial behaviors and psychopathy (73-82). These investigations indicate that, when individuals with psychopathy imagine or observe others in pain, brain areas necessary for feeling empathy and concern for others (e.g., dorsal anterior cingulate) are less activated or fail to become active, and connections between these regions and other important regions involved in affective processing and decision-making are weaker than in the normal population.

Diminished response to cues of threat or punishment have been hypothesized to mediate the failure to learn from punished responses, the callous exploitation, the lack of remorse, and the focus on immediate rewards that characterize psychopathy. Consistent with this notion, an fMRI investigation revealed that the limbic–prefrontal circuit (involving amygdala, orbitofrontal cortex, anterior insula, and anterior cingulate cortex) that was activated during fear conditioning (using slides of neutral faces) in normal individuals was not activated in psychopaths (83).

Relatedly, psychopathy has been associated with deficient autonomic responding in anticipation of threatening events (84) and inhibited startle to negative emotional stimuli (e.g., victim scenes) (85). Prefrontal functional impairments have been proposed to relate to the behavioral and affective deficits seen in psychopathy (86), as structural studies suggest that antisocial personality disorder is associated with reduced prefrontal gray matter volume and that these prefrontal gray deficits are reflected in diminished electrodermal responses (87).

Hicks et al (88) investigated the hypothesis that primary psychopathy (affective-interpersonal features) is predominantly heritable, whereas secondary psychopathy (social deviance) is primarily environmentally determined. Trait-based indices of primary and secondary psychopathic tendencies were assessed using the Multidimensional Personality Questionnaire (MPQ) to estimate fearless dominance and impulsive antisociality, respectively, and the environmental contexts of family, school, peers, and stressful life events were also evaluated. MPQ impulsive antisociality was primarily associated with environmental risk factors, and these environmental influences were greater than for MPQ fearless dominance. However, MPQ fearless dominance and impulsive antisociality exhibited similar heritability, and genetic effects appeared to mediate the associations between MPQ impulsive antisociality and environmental contexts. The authors concluded that gene-environment interactions rather than main effects of genes and en-

vironments may account for the differential environmental correlates of primary and secondary psychopathy.

In sum, recent investigations of differences between patients and controls in the neural underpinnings of empathy to other's pain have been especially informative. Social neuroscience research in this area is still nascent, however, as the number of specific component social processes whose neural and genetic mechanisms have been investigated in patients and controls remain quite limited.

Hypoactive sexual desire disorder

There is now a sizeable literature in psychiatry and psychology on female hypoactive sexual desire disorder, which is defined in the DSM-IV as "persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity" that cause "marked distress or interpersonal difficulty". Epidemiological studies report that about 40% of American women between 20 and 70 years of age have problems with low sexual desire (89). The disorder has a negative impact on quality of life of both the individual and the couple (89-91).

Social neuroscientists have begun to investigate hypoactive sexual desire disorder because of the importance of understanding the brain regions and networks involved if new and more effective interventions are to be developed. Although this is still a nascent area of research, the extant work suggests the importance of central, in contrast to peripheral, processes in both healthy individuals and patients (92), and the brain regions and networks associated with sexual desire vs. love are beginning to be identified.

In healthy subjects, recent neuroimaging studies have shown that sexual desire involves not only emotion-related limbic areas, such as the amygdala, hypothalamus, hippocampus, ventral striatum, and insula, but also a distributed cortical network including (but not restricted to) three main areas: anterior cingulate, parietal lobule, and middle temporal gyrus/posterior superior temporal sulcus (93). The distributed nature of this network in healthy subjects highlights how sexual desire involves brain areas that mediate different functions, such as reward mechanisms (e.g., ventral striatum) and higher-order cognitive processes associated with social cognition, self-representation, body image, and attention (94). Together, the functions of this brain network support the view of sexual desire as a phenomenon driven not only by bottom-up influences but also top-down influences from past and integrated rewarding bodily self-related experiences, combined with sensory (e.g., visual) and emotional processing (93,94).

Neuroimaging studies in people with sexual desire disorders constitute a unique opportunity to investigate the putative role of these underlying brain processes (95-98). Using PET, Stoleru et al (95) demonstrated differential brain activation to visual erotic stimuli between men with hypoactive sexual desire disorder and healthy men. Whereas healthy men showed decreased activity in the medial orbitofrontal region, men with the disorder showed no such decreased activity to the erotic stimuli. The authors interpreted this difference as due to the maintenance of inhibitory control when men with the disorder viewed erotic stimuli. Men with hypoactive sexual desire disorder, compared to controls, also displayed greater deactivation in emotion-related brain regions (such as the anterior cingulate) and in brain regions mediating motor imagery processes, somatic experiences, and self-representation (e.g., the secondary somatosensory cortex).

Subsequent neuroimaging studies in this field, performed with fMRI and female participants (97,98), reinforced Stoleru's findings. In brief, these studies revealed two distinct types of neural changes in participants with hypoactive sexual desire disorder relative to healthy controls. Women with the disorder showed a hypoactivation in the sexual desire brain network that is typically activated in healthy participants (e.g., posterior insula); and a hyperactivation in three specific brain regions that are not typically activated in healthy participants: the inferior parietal lobule, inferior frontal gyrus, and extra-striate visual cortex.

This is in line with current hypotheses about reduced sexual desire (99), which suggest that hypoactive sexual desire disorder may result from hypofunctional excitation, hyperfunctional inhibition, or some mix of the two. Interestingly, these findings also echo Masters and Johnson's, Kaplan's and Barlow's clinical concept of "spectatoring" (100,101), which assumes that deficits in sexual functioning may be (at least partly) associated with inhibited excitement due to a disruption in the processing of erotic stimuli and a shift in attentional focus from erotic stimuli to self-monitoring of sexual response (i.e., self-focus attention).

This hypothesis needs further testing, but these results provide insights into the brain processes underlying sexual desire disorders as well as anomalies in social information processing in hypoactive sexual desire disorder. More generally, this work illustrates the potential value of social neuroscience – from analyses of regional brain activity to the dissection of component social structures and processes – to better specify the mechanisms underlying a mental disorder and to develop more proximal and effective targets (e.g., pharmacologic, neural, cognitive, social) for intervention.

FUTURE PERSPECTIVES

The human brain is among the most complex biological structures known. Given the complexity of the brain and its outputs, what is perhaps remarkable is that the appearance of a mental disorder across a lifetime is not more common. The original focus on the genetics and neural regions associated with psychiatric diagnostic categories was an important initial step, but such an approach assumes that these categories can be mapped in a 1:1 fashion to specific underlying causes. Given the complexity of the human brain and the vagaries of mental disorders, it is

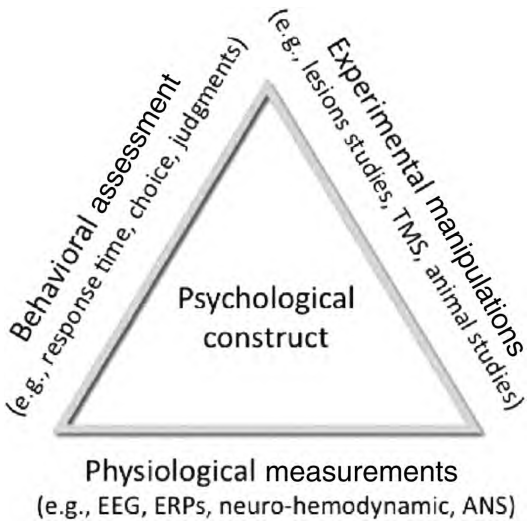

Figure 1 The golden triangle of social neuroscience research. EEG – electroencephalogram, ERPs – evoked response potentials, ANS – autonomic nervous system, TMS – transcranial magnetic stimulation

not surprising that targeting specific endophenotypes within each mental disorder is proving to be more informative. This research is gaining momentum, with the list of biological and behavioral intermediate phenotypes increasing rapidly. Given that among the most important functions of the human brain are the production of an organized mental existence and the orchestration of behavior, including our recognition and interaction with others, it may prove informative to also specify the component social structures and processes that are involved in mental disorders.

Correlating complex mental disorder with regions of activation in the brain is only a preliminary step toward specifying the brain mechanism responsible for any such disorder. The brain does not operate exclusively at the spatial level of molecules, cells, nuclei, regions, circuits or systems, nor does it operate exclusively at the temporal level of milliseconds, seconds, minutes, hours or days. Any single neuroimaging methodology provides a partial view of brain activity within a very limited range of spatial and temporal levels. Therefore, converging methods that gauge neural events at different temporal and spatial scales should be used to provide a more complete picture of brain function.

The equilateral triangle depicted in Figure 1 represents the equal importance of three converging approaches that may help us to understand the brain mechanisms underlying mental disorders (102): a) behavioral assessment, or the specification of component information processing operations, including specific component social processes; b) experimental manipulations; and c) physiological measurements. Neuroimaging is a correlative measure, so experimental studies including lesion, transcranial magnetic stimulation and pharmacological interventions (e.g., ligands, drugs) in human and nonhuman animal are essential to further elucidate the causal role of any given neural structure, circuit or process in a given task. Each of these angles has limitations, but the confluence of the three can facilitate advances in our understanding of the neural mechanisms underlying mental disorders.

CONCLUSIONS

Technological and computational developments over the past few decades have transformed the nature and amount of data available on brain structure and function at various scales. However, with these advancements have come distinctive methodological, analytical and conceptual frameworks, and increased subdisciplinary specialization, interests and pressures toward segregation. Although understandable, this specialization can work against the integration of data across levels of analysis, especially when it is associated with eliminative reductionism rather than constructive reductionism, which favors the study of the part to better understand the whole. A contribution of the multilevel integrative approach of social neuroscience to psychiatry may therefore be the way in which data at various levels of organization of brain function and behavior (including social behavior) are related to one another.

Although not unique in psychiatry, social neuroscience may represent a hospitable meeting ground articulating and integrating theories, methods and data from various levels of organizations and disciplinary perspectives to better understand the causes and treatment of mental disorders. Moreover, psychiatry has been split into two subdisciplines, one focused on pharmacological and biological treatment of disease and the other focused on talk therapy. Social neuroscience may serve as a meeting ground between these perspectives, as well as one in which pharmacological intervention could be viewed as a strategy for improving social function.

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Social neuroscience: bringing an end to the destructive and misguided "social" versus "biological" in psychiatry

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Psychiatry is the branch of medicine that demands the most careful appreciation and understanding of social, as well as psychological and biological, aspects of patients and their health problems. For many psychiatrists, this complexity is at the heart of the medical specialty's appeal.

However, this reality also provides a challenge that has resulted in entrenched positions being adopted by some professionals and members of the lay public, who view clinical issues and entities in a simplistic, polarized way as being *either* "social" *or* "biological" in nature and origin. Such thinking is often driven by politics and ideology and it is a major impediment to public understanding, professional relationships, development of effective services, and, crucially, to patient care (1).

Any experienced psychiatrist knows that excellent care involves careful and skillful attention to biological, psychological and social issues and that in any particular clinical case these are commonly intertwined in a way that does not allow simple reductionism. Indeed, dealing with this complexity in a pragmatic, clinically effective manner is the core business of psychiatry.

Set within this clinical and scientific context, it is, therefore, a pleasure to read the paper by Cacioppo et al (2), which focuses on the developing field of social neuroscience and the potential contributions it can make to psychiatry. The paper is clear and well-balanced and the main arguments in favour of the relevance and importance of social neuroscience for psychiatry are persuasive.

The concept of social neuroscience was introduced early in the "Decade of the Brain" (the 1990s) and brings together the increasingly powerful tools of neuroscience to explore the brain mechanisms that underlie social interactions and behaviors (3). At a theoretical level, it makes enormous sense to put effort into understanding the neuroscience of social behavior in both its normal forms and when impaired within the context of psychiatric illness. At an empirical level, there are many interesting findings emerging that point to a bright future for this field.

Together with the overlapping and similarly rapidly developing fields of cognitive neuroscience and affective neuroscience and with improving tools like functional imaging and molecular biology, social neuroscience has a great deal to offer for further understanding of many of the clinical problems experienced by psychiatric patients. Together, these are areas that will bridge the gap between the molecular and biological systems and the complex experiences of the patients we see in the clinic.

It can be expected that these approaches will allow a reconceptualization of the major clinical entities in psychiatry that will allow movement away from crude diagnostic classifications based on symptom descriptions and towards diagnostic approaches that are based upon the normal and abnormal workings of the brain and which are supported by laboratory tests, as is usual in other branches of medicine (4,5).

We must, of course, be realistic about time scales and what can be achieved. Whilst being appropriately optimistic, it is important to be aware of the challenges and be cautious in accepting early findings too readily even if those findings have tempting plausibility. The acid test in science is independent replication and confirmation through convergent, complementary experimental approaches. Many studies in the neuroscience literature are substantially underpowered, which has the undesirable result that many of the published results that are "nominally significant" will actually represent false positives (however plausible they appear) (6). Thus, as has been the case in molecular genetics (7), there will be a need for large samples (probably thousands rather than the tens of participants that are common in many neuroscience studies published to date), collaboration between researchers and an emphasis on independent replication.

Cacioppo et al raise the intuitively plausible point that so-called "endophenotypes" are likely to be genetically and biologically simpler to study than a psychiatric disorder itself. To date, genetic studies have not shown this to be the case (8). Thus, whilst it may prove to be the case, there is not yet persuasive evidence to support the assertion. Indeed, a substantial body of research experience backed up by theoretical work and common sense suggest that no approach to unraveling the complexity of causation and triggering of psychiatric illness will be easy – and social neuroscience is most unlikely to be an exception.

An area not highlighted by Cacioppo et al that will be important to understanding the normal and abnormal working of the brain relates to large-scale computer modeling. For example, the Human Brain Project, funded by the European Union, seeks to model

the development of neuronal networks and understand emergent properties using intensive computing for bottom-up modeling of human brain function (9). The hope is that this project, which focuses on multilevel integration, will help to build the foundations that are needed to reconstruct and simulate the human brain and its diseases. Together with other large-scale initiatives in neuroscience (9), such approaches are likely to improve understanding of psychiatric illness.

In conclusion, social neuroscience has much to offer over the medium to longer term in improving understanding of complex aspects of psychiatry. In the shorter term, it can be expected that the very existence of the field will help to combat the annoyingly persistent and wholly unhelpful naïve "either/or" thinking about mental health that categorizes things as being "social" or "biological". That will be of enormous benefit to psychiatry and its patients.

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Will better psychiatric treatments emerge from top-down or bottom-up neuroscientific studies of affect?

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Cacioppo et al (1) discuss how the emerging social neuroscience perspective may promote understanding and treatment of psychiatric disorders. They argue that all these disorders are embedded within social structures that strongly influence our thoughts and feelings.

This is true. Still, it remains ambiguous how top-down enculturated perspectives to human minds will yield fundamental insights to psychiatric therapeutics beyond what psychiatry has already achieved. Aside from debatable attractions of modern brain imaging, embraced finally by psychological sciences, how might social neuroscience provide new psychiatrically useful perspectives that are not already reasonably well developed in biological psychiatry?

Certainly it is wonderful that social psychology is finally studying the brain, with many unique contributions, such as illumination of brain substrates of empathy (e.g., 2). Still, an enormous challenge for human social neuroscience is to provide new therapeutics. Another is for social and affective neurosciences to coordinate their efforts, especially better integration of top-down social and bottom-up neuroevolutionary perspectives. Such work remains rare.

I was delighted that Cacioppo was among the first to adopt my 1998 text *Affective Neuroscience: The Foundations of Human and Animal Emotions* (3) for classroom use. That vision served as one springboard for his advocacy of "social neuroscience", which followed historically upon "social psychophysiology" initiatives (4). But it would be useful to more fully harmonize top-down, human focused approaches with bottom-up cross-species affective neuroscience ones. Integration of knowledge bases is essential to minimize the likelihood of related approaches talking past each other, and promoting splintering that was common in 20th century psychology.

How shall we integrate diverse neuroscience approaches to yield new psychiatric insights? Clearly, investigators of human and animal emotions need to seek unified research strategies, with neuroevolutionary issues being a centerpiece, while not emulating many flaws of modern evolutionary psychology, with speculations about the evolution of human cortico-cognitive tendencies, that remained unintegrated with cross-mammalian affective processes (5).

Likewise, many issues that concern human social neuroscience are emergents of social learning, that remain

tethered to cross-mammalian affective underpinnings. Unfortunately human social neuroscience has no substantive access to such issues without invasive brain research. How is this dilemma to be solved? I believe this question is critical for the impact that human social neuroscience can have on fundamental psychiatric issues. Novel psychiatric treatments cannot be found without a constitutive biopsychological understanding of core affective processes.

This issue will require fuller cross-species integration, especially from neurosciences that are heavily invested in fundamental mammalian social emotional/motivational processes. Animal brain research is essential for clear visions of evolved origins of the human mind, since it provides access to primary-process brain-affective mechanisms upon which consciousness itself is still grounded (3,6). Top-down human approaches simply cannot achieve that with comparable scientific rigor. On the other hand, it may be wise to envision the socially-constructed cognitive subtleties of the human mind, that arose from the rapid evolutionary expansion of human neocortex, upon which learning, rather than evolutionary modularization, "stamps" the diverse functional specializations (7).

Thus, to advance psychiatric thought, a key issue for human social and cognitive neurosciences should be (without resurrecting an outdated nature-nurture debate): to what extent are the adult neocortical functions of human beings due to evolutionary selection as opposed to social construction? The subcortical instinctual functions of mammalian brains are clearly inherited. The local regional circuitry of neocortical columns is also certainly constrained by strong evolutionary underpinnings, as are many of the looping intracortical connections, but this does not mean that either prescribes functions as opposed to offering potentialities (depending on subcortical inputs). Clearly, most neocortical functions are developmentally rather than evolutionarily programmed (7). This has profound implications for the fecundity of a human-oriented social neuroscience that has little access to fundamental issues.

All mammals are close evolutionary relatives with regard to subcortical affect and motivation networks and their vast mind-supporting, consciousness-creating neural networks and chemistries. Although abundant genetic polymorphisms code brain chemistries – from transmitters to receptors to all the intermediate neuronal housekeeping processes – the bottom line is simple: we humans are not special in the types and neurogeographical distributions of our genetically selected brain circuits and their neural chemistries, an understanding of which will lead the way to new psychiatric therapeutics.

For human social neuroscience to have substantial impact on human psychiatric therapeutics, it needs insights from affective neuroscience approaches that can access the actual neural mechanisms of the affective mind. For instance, the fundamental psychological-pain mechanisms that mediate separation-distress in mammals are clearly self-similar (3), potentially allowing us better medical treatments of depression than behavioral and cognitive approaches of the past have provided (e.g., 8-11). So, when we speak about human loneliness and social bonding, our understanding of the underlying raw affects may be illuminated more by animal studies than by human ones (12,13), a key strategic issue social neuroscience would be wise to consider.

I look forward to a human social neuroscience that becomes fully integrated with the affective neurosciences that have long dealt with issues of psychiatric interest. We now need better two-way communication among the human and animal neurosciences. Our own efforts to link cross-species affective neuroscience findings to fundamental human psychiatric issues can be found in Panksepp (3) and Panksepp and Biven (14).

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Social neuroscience and mechanisms of risk for mental disorders

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In their thoughtful paper, Cacioppo et al (1) emphasize the role of social neuroscience as an integrative meeting ground of a variety of methodological approaches, "neural, hormonal, cellular, molecular and genetic", and call for a truly "interdisciplinary" approach. We fully endorse this viewpoint and would like to emphasize the importance to apply this strategy at another important, but underexamined juncture between disciplines: the connection between psychiatric epidemiology and psychiatric neuroscience. Specifically, we propose that there is growing evidence that an important facet of risk for severe mental illness can be understood as altered neural processing of specifically social stimuli, and that this may have therapeutic and preventive applications in the future.

It is well known that impoverished or abusive social contexts contribute to the risk for mental illness (2). Recent work also supports the view that epidemiologically validated risk factors such as urban living and upbringing and migration have a social component, as proposed by the social defeat hypothesis (3). Specifically, work from our laboratory has suggested a specific impact of social stress on activation in a perigenual cingulate-amygdalar circuit in healthy populations exposed to urban living and upbringing (4) and migration. Since previous work, as highlighted by Cacioppo et al, has shown that the same circuit is impacted by (serotonergic) candidate genes that show gene-environment interactions (5,6), we have recently proposed that this circuit, the limbic regions (such as ventral striatum and hippocampus) linked to it, and regions of evolutionarily more recent medial and lateral prefrontal cortex that regulate it, may be a core convergence pathway for risk for mental disorders arising through social stressors (7). In fact, given preclinical evidence, it also appears possible that socially adverse environments early in brain development are causal for the dysfunction specific to social stress observed in adults exposed to risk. Since this circuit and those linked to it are found abnormal and related to symptomatology in patients (as demonstrated by the three clinical conditions discussed by Cacioppo et al), they may also be important for treatment. Seen this way, the social environment remains relevant throughout the trajectory of mental illness, as it is configured, unfolds and gets addressed. Clarifying these interacting genetic, neural and environmental mechanisms further is thus important for therapy, and possibly even prevention.

This suggests an ambitious, but actionable work program spanning several layers of description. Evidence for mechanisms supporting gene-environment interaction on the systems level should be supplemented by research to clarify its cellular basis in humans. This is challenging as the primary tissue of interest is not available in man, but methods such as genome wide methylation analysis in peripheral tissues may help to identify some of the genes and pathways modified by social environmental stress (8). A further level of description may be added through the study of human neurons derived through induced pluripotent stem cell technology (9), although most epigenetic programming is removed in the process of generating these cells. Gene-environment interaction effects in brain should be confirmed directly by combining social exposures with imaging in genotyped subjects.

Based on these data, the neural underpinnings of subcomponents of the social environment that could contribute to the epidemiological evidence we have highlighted need to be analyzed further (examining effects such as social defeat, discrimination, and loneliness – as emphasized in Cacioppo et al's paper). This will require close interactions with the social sciences in providing scales that measure these facets of the social landscape with precision. In addition to laboratory paradigms, this will also require field studies that combine neuroimaging and biomarker ascertainment with experience-based assessment, mobile neuropsychological testing and tracking of subjects in spatially and socially well defined real-life contexts (10).

Based on epidemiological evidence that time periods such as the perinatal period, early childhood and adolescence are especially vulnerable for these environmental exposures, an account must be developed on which neurobiological changes underlie vulnerability across the lifespan. This requires longitudinal and ecological human studies that combine neuroscience approaches with the power of epidemiological methods, such as the European IMAGEN study (11). We have recently begun a study that uses these methods combined with imaging and urban geography to highlight aspects of the urban social environment.

A better understanding of these neural circuits will also enable back-translation into a generation of more specific animal models that can be used in early drug discovery (12), and could enable the identification of molecular targets for social dysfunction through cellular and (epi-)genetic approaches. Further into therapy development, this neuroscience information can also constrain pharmacological and psychotherapeutic strategies targeting the identified circuits. For example, the prosocial neuropeptides oxytocin and vasopressin can be shown to act on precisely the core perigenual cingulate-amygdalar regulatory circuit for gene-environment interaction, and

common genetic variants in the brain receptors for these prosocial neuropeptides modulate the activity and even structure of these regions in humans (13). As we have recently discussed for the specific case of oxytocin in combination with behavior therapy (13), this opens up a mechanism-guided approach for interfacing the usually separate domains of biological and psychological therapies, as predicted at the conclusion of Cacioppo et al's paper. As emphasized in that paper, a truly interdisciplinary approach to social neuroscience in psychiatry has therefore much to offer for people suffering from mental illness, their clinicians, and science.

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The brain's intrinsic activity and inner time consciousness in schizophrenia

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How is it possible that the brain's neural activity is directly dependent upon environmental contingencies? This is a central question raised by Cacioppo et al's impressive target paper (1), which I will tackle here by bringing in a novel perspective, the brain's intrinsic activity.

C. Sherrington, the British neurologist working at the beginning of the 20th century, considered the brain a mere passive sensorimotor reflex apparatus. Extrinsic stimuli from the environment trigger neural activity in pathways that result in sensorimotor reflexes. This extrinsic view of the brain has been challenged by authors such as G. Brown, K. Lashley and R. Llinas, based on the observation of intrinsically generated activity in the brain (2).

The recent discovery of high resting state activity in a particular set of brain regions, the default-mode network, has once again raised the question of an intrinsic view of the brain's neural activity (3). Since its initial description, the functions of that network have been debated and associated with the self (4) and consciousness (5-9).

What remain unclear, however, are the exact neuronal features of the resting state itself that make possible its interaction with extrinsic stimuli from the world. These neuronal features must be intrinsic to the resting state while at the same time predisposing the brain to the association of its stimulus-induced activity with consciousness and self. We may thus need to develop an intrinsic-extrinsic interaction model with regard to the brain.

The term intrinsic activity describes spontaneous activity generated inside the brain itself (10,11). Since the observation of spontaneous activity implies the absence of extrinsic stimuli and is thus mere rest, the term intrinsic activity is often used interchangeably with resting state activity, especially in an experimental-operational context (10).

One recent proposal suggests that the resting state's slow wave fluctuations in frequency ranges between 0.001 and 4 Hz are central in yielding consciousness (3,5,12). Due to the long time windows of their ongoing cycles, i.e., phase durations, these slow wave fluctuations may be particularly suited to integrating different information. Such information integration may then allow for the respective content to become associated with consciousness (7,9).

Spontaneous fluctuations of neural activity in the resting state are often observed, especially in the default-mode network, where they are characterized predominantly by low frequencies

(<0.1Hz). However, low (and high) frequency fluctuations in neural activity can also be observed in regions other than that network, such as the sensory cortices, motor cortex, insula, and subcortical regions like the basal ganglia and thalamus. Rather than being specific to the default-mode network, low frequency fluctuations appear to be a hallmark feature of neural activity in general.

It is apparent, then, that there is a complex temporal structure and organization to the brain's intrinsic activity. Most importantly, this temporal structure seems to bridge the temporal gaps between different discrete points in time. By linking together neural activities at different points in time, a certain degree of temporal continuity in the brain's intrinsic activity is constituted.

In some psychiatric disorders, abnormalities in the spatiotemporal continuity of both intrinsic activity and consciousness have been described.

Instead of providing a grid or template of spatiotemporal continuity, "inner time and space consciousness" in schizophrenia seems to be characterized by spatiotemporal fragmentation and disruption. These patients no longer experience temporal continuity and thus a dynamic flow of time (and space) in their consciousness. Instead, the stream of consciousness is disrupted and blocked with the three temporal dimensions of past, present and future being disconnected from one other.

The glue between the different discrete points in physical time seems to be missing in the consciousness of time and space. This implies that the different contents, including their distinct discrete points in physical time and space, can no longer be linked to each other in the consciousness; the glue and thus the spatiotemporal continuity is lost. This is very apparent, for instance, in the following quote of a patient with schizophrenia (13): "When I move quickly, it is a strain on me. Things go too quickly for my mind. They get blurred and it is like being blind. It's as if you were seeing a picture one moment and another picture the next".

The patient describes here that the contents of his consciousness, the different pictures, are no longer linked together. There are no longer any transitions between the different discrete points in time and space associated with the different pictures. The pictures are, as it were, experienced as pearls without an underlying chain. Since the underlying chain – the spatiotemporal continuity – seems to be disrupted within itself, the pearls can no longer be put together, ordered, structured and organized in consciousness.

In other words, both the "inner time and space consciousness" and "consciousness of contents" become disordered and disorganized, leading to what may be described as *spatiotemporal disruption*. This leads the patient to experience the contents of consciousness in an abnormal way, as is manifested in many of the schizophrenic symptoms such as ego disorders, thought disorders, hallucinations and delusions.

Numerous studies have recently shown resting state abnormalities in schizophrenia (e.g., 14). Changes in gamma oscillations (and low delta oscillations) have been reported (e.g., 15), indicating abnormal temporal continuity in the brain's intrinsic activity. Much, though, remains unclear at this point. First, the exact nature of these spatial and temporal resting state abnormalities remains to be established. Secondly, their link to the above-described phenomenal abnormalities in the consciousness of time and space in these patients is not clear at this time.

The extrinsic stimuli may encounter an already altered temporal and spatial continuity when interacting with the brain's intrinsic activity. The latter's spatial and temporal abnormalities may be imposed upon the extrinsic stimuli, which are then experienced in abnormal spatial and temporal ways in consciousness. This in turn may account for some of the characteristically difficult symptoms of sufferers of schizophrenia, that could ultimately be described as abnormal spatiotemporal constellations between intrinsic activity and extrinsic stimuli – in short, abnormal rest-stimulus interaction. However, much work remains to be done to establish direct links between the neuronal and phenomenal levels in these patients.

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Social neuroscience in psychiatry: pathways to discovering neurobiological risk and resilience

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Cacioppo et al (1) provide a thoughtful overview of the ways in which social neuroscience can significantly advance our understanding and treatment of mental disorders.

They touch on the way gene regulation, epigenetics and the environment can alter neurodevelopmental trajectories and in turn influence social behavior and social functioning. We would like to emphasize here the importance of future research exploring dynamic social brain changes taking place during adolescence (2,3) as a possible key to understanding the emergence of mental disorders at this critical stage of maturation, when risk for such disorders peaks.

Recent work in our laboratory shows that attenuated growth of the hippocampus and attenuated reduction in putamen volume during age 12 to 16 years are associated with the onset of depression (4). Sex is also a significant factor, since exaggerated amygdala growth in females and attenuated growth in males seems to increase the risk of depression. Taking account of the neurodevelopmental background for boys and girls, relevant to all aspects of cognition, including social cognition, is a necessary prerequisite to understanding mental disorders and their neurobiology.

The prominence of social themes in the characterization of autism spectrum disorders (ASD) also warrants brief discussion. Our recent work on ASD (5) is relevant in being an interdisciplinary study involving biology and engineering, and in linking statistical approaches to biology. Importantly, while the emphasis of most studies has been on discovery of neurobiological risk markers for such disorders, in our study we also identified several single-nucleotide polymorphisms (SNPs) that protected against ASD, that is, might be associated with resilience to development of the disorder.

For example, we found that the SNP rs12317962 protected against ASD (5). This SNP lies in the gene KCNMB4, encoding a potassium channel involved in neuronal excitability, which is highly expressed in the fusiform gyrus and key social brain regions, namely the superior temporal, cingulate and orbitofrontal cortices. Other SNPs, such as variation in rs3796863 in CD38, a gene linked to ASD and known to be involved in oxytocin secretion, has also been linked with activation of the amygdala and in particular the fusiform gyrus, during visual processing of social stimuli in healthy young men (6). We are in the processes of furthering this research in ASD by examining the influence of allelic variation on brain regions using neuroimaging.

Schizophrenia is another disorder that involves deficits in social cognition. Recent theories propose that aberrations in dopaminergic and glutamatergic subcortical-amygdala-prefrontal circuits give rise to dysregulation of salience signaling, causing impairments in emotion-related perception, learning and memory (7), similar to the model of Phillips et al (8) described by Cacioppo et al (1) in the context of depression.

Interdisciplinary research of Walter et al (9) shows that carriers for the psychosis risk variant of the SNP rs1344706 (gene ZNF804A) have abnormal neural activation in the medial prefrontal and left temporo-parietal cortex, as well as in regions of the mirror neuron system, during a theory of mind task. This potential intermediate phenotype derived from functional imaging may have implications for biological treatment of social cognitive impairments in schizophrenia.

One thing that is clear from Cacioppo et al's paper (1) is that, across disorders, common social brain regions are dysfunctional: the amygdala, orbitofrontal cortex, medial prefrontal cortex, superior temporal sulcus, anterior insula and anterior cingulate. Yet, the way in which they deviate from normal functioning (hypo- vs. hyper-activation/mixture of both) depends on the illness being studied and the social processes in question. Therefore, we should study not only across disciplines but also across mental disorders, and in the context of carefully controlled treatment interventions, to provide insights into both risk and resilience factors associated with developing particular disorders.

Oxytocin has been proposed as a potential adjunctive treatment for the social cognitive and behavioural deficits common in social anxiety disorder, ASD, schizophrenia, and borderline personality disorder (10). While there are several oxytocin-related risk alleles that have been linked to social brain functioning, there is little insight into the mechanisms of the actions of oxytocin in the brain. This is a promising avenue for future research in psychiatry.

In conclusion, Cacioppo et al's paper on social neuroscience and mental disorders provides us much food for thought. There is a need for dynamic interdisciplinary (rather than just multidisciplinary) exchange between biological and other sciences; assessing changes in trajectories of brain structure and function; linking these dynamic changes to genes that may bestow risk or resilience to development of illness; and examining the impact of interventions that modulate social

cognition. All of these approaches and their combination present exciting ways forward in understanding some of the most challenging and complex disorders affecting human beings.

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Social neuroscience in psychiatry: of obvious relevance

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Cacioppo et al (1) make the important point that the study of normal and abnormal social behavior is essential in the understanding of mental disorders. Indeed, it is hard to imagine a mental disorder that does not involve, or lead to, abnormalities in social interaction. One could even say that one of the hallmarks of mental illness is that social interactions are affected. Obviously, and as argued by many, the human species is a social species and therefore its brain is developed to support social activities.

The paper provides three examples of psychiatric disorders where abnormalities in social functioning are involved: major depressive disorder, antisocial personality and hypoactive sexual desire disorder. However, the relationship between abnormal social activities and these three disorders may be quite dissimilar. One could argue that in major depression the abnormalities in social interactions are secondary to the disease and may therefore be important in treatment and rehabilitation but not as important in understanding the etiology of the illness (2). In contrast, antisocial personality disorder is characterized at its core by abnormal social interaction, where the abnormality may be lifelong and of a developmental nature. Finally, hypoactive sexual desire disorder may lead to social interaction abnormalities, but these may not be the cause of the illness.

The authors mention, but do not address in detail, two other mental disorders where abnormal social interaction, specifically impaired social cognition, may be a root cause of the illness: autism (3) and schizophrenia (4).

Emotional and cognitive dysfunctions are the core clinical features of schizophrenia (5). Moreover, it has been argued that impairments in emotion recognition and theory of mind (ToM) may even trump the value of general cognition and symptoms in explaining outcome in schizophrenia (6).

In healthy individuals, social cognition has been extensively studied using functional and structural imaging, and a network of brain regions subserving it has been identified (7). In short, the processing of facial expressions depends critically on the amygdala and the orbitofrontal cortex, whereas in mentalizing tasks, such as ToM, the medial and orbitofrontal cortex is critical (8).

In schizophrenia, functional neuroimaging studies have consistently demonstrated reduced activity of the amygdala during processing of facial emotions compared to healthy controls (9), and reduced activation of the prefrontal cortex (PFC) has been related to impaired performance on ToM tasks. Indeed, a recent meta-analysis of functional imaging studies, comprising 450 schizophrenia patients and 422 healthy controls, has shown reduced amygdala and PFC activity in social cognition in schizophrenia (10).

In contrast to the numerous functional neuroimaging studies in schizophrenia, only few structural imaging studies have investigated the relationship between abnormalities of the amygdala and PFC and social cognitive deficits seen in patients. So far, samples have been small (between 16

and 38 patients), and the influence of IQ and symptomatology has often been disregarded.

We recently completed a study where we investigated whether social cognitive deficits in patients with schizophrenia are related to gray matter volume abnormalities of the amygdala and PFC. We assessed facial emotion recognition and ToM in 166 patients with schizophrenia and 134 healthy controls, and magnetic resonance imaging brain scans were acquired. Preliminary results suggest that reduced PFC, but not amygdala, gray matter volume is associated with social cognitive deficits in schizophrenia (11). Thus, anatomical abnormalities in schizophrenia may in part be related to social cognitive dysfunction. Whether this is specific to schizophrenia or these anatomical changes are also observed in other disorders characterized by social deficits remains to be studied.

All in all, Cacioppo et al's paper makes a very important and compelling case that social neuroscience should be integrated into psychiatry and may make important contributions in understanding the etiology and sequelae of mental disorders. However, there is a lot of pioneering work that needs to be done to start understanding the role of this important human aspect in the etiology and course of psychiatric illness.

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Bridging psychiatry and neurology through social neuroscience

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Social neuroscience launched a novel multilevel (neural, hormonal, molecular and genetic) explanation of social cognition in psychiatry. In particular, the use of different levels of scientific inquiry assessing a) behavioral social cognition sensitivity to psychiatric impairment, b) neural networks engaged in social behaviors, c) the genetic underpinning of social phenomena, and d) the influence of the social environment on biological processes, have been outstandingly addressed by Cacioppo et al's paper (1).

Neuroscientific progress suggests that the separation between psychiatry and neurology is counterproductive. Classical neurological conditions present a range of social cognition impairments that are often underrecognized and frequently undertreated. Social neuroscience has made important progress in elucidating the neurobiology of the social brain, but has not focused sufficiently on neurological disorders. Here we consider the implications of social neuroscience research for a specific neuropsychiatric condition, the behavioral variant of frontotemporal dementia (bvFTD). Moreover, we highlight the importance of social neuroscience for the cross-talk among psychiatry and neurology.

BvFTD is a neurodegenerative disease whose initial symptoms are often confused with several psychiatric conditions. It is characterized by early decline in social interpersonal behavior, personality changes, and progressive deterioration in social functioning (2). Conventional neuropsychological assessment as well as clinical routine neuroimaging have been not been very useful for early diagnosis (2). The social neuroscience approach has raised new opportunities for research and translational applications in bvFTD.

First, social cognition assessment in bvFTD has allowed the detection of early and subtle behavioral impairments, appearing even before imaging signatures of brain atrophy, or a clear decline in formal cognitive status (3). In particular, social cognition tasks that resemble everyday behavior seem to be a far more adequate assessment for this purpose (4). Social cognition assessment may soon become part of the clinical screening for bvFTD.

Second, it has been proposed that models of social cognition associated with a degeneration of the fronto-insulo-temporal (social context network model) or fronto-insular (salience network) regions may explain the myriad of bvFTD social cognition impairments (2). For instance, Von Economo neurons are large spindle-shaped cells, abundant in the insular and anterior cingulate cortex. Among primates, these neurons have evolved only in hominids, and seem to be particularly vulnerable in neuropsychiatric conditions resulting in social cognition impairments. In bvFTD, a specific loss of these neurons within fronto-temporo-insular atrophy, at early stages, has been associated clinically with changes in empathy, social awareness, and other social cognition domains (5).

Third, an important genetic component of bvFTD has been related with social cognition impairment. There are three main genes for bvFTD: MAPT, GRN, and C9ORF72. Patients with C9ORF72 mutations exhibit widespread frontotemporal atrophy, associated with psychiatric presentations as well as with social neglect (6). In a similar way, animal models and clinical studies of GRN have shown early social and emotional changes, without gross impairment in overall health (6).

Fourth, the potential role of the social world, and its interaction with brain changes in bvFTD, deserves consideration. For instance, feeling lonely is associated with increased risk for dementia (7) and with a wish to hasten death in FTD (8).

An inter-level social neuroscience approach combining the study of social behavior, neural networks, genetic influences, and the interactions between social behaviors and social cognition would help to provide a more in-depth understanding of bvFTD, as well as of the overlaps of this disorder with the symptomatology and social cognition impairments of several psychiatric conditions (9). A new form of cross-talk between psychiatry and neurology may thus be developed in the social neuroscience arena, spearheaded by work on bvFTD as perhaps the clearest example of the bridges between the two disciplines.

Stimulating this cross-talk between neurological and psychiatric research seems to be one of the most promising roles for social neuroscience. Several neurological conditions with mental health manifestations (e.g., neurodegenerative conditions, prosopagnosia, tuberous sclerosis, and Angelman, Heller, Prader-Willi, Williams, Turner and Klinefelter syndromes) present impaired social functioning (10). Here, we have highlighted the multilevel social neuroscience approach to bvFTD, but the understanding of several other neurological conditions could benefit from this approach.

Many social cognition domains (social emotions, decision making, theory of mind, empathy, moral cognition, and social norms) may be impacted differentially in various psychiatric and neurological conditions, and the differences in such parameters could be built into technologies for diagnosis and measurement of treatment efficacy.

Psychiatrists and neurologists within this novel social neuroscience approach may be able to contribute a powerful multidisciplinary and transdisciplinary approach (11), that would be both clinically and theoretically relevant to major advances in contemporary neuropsychiatry.

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Loneliness and social neuroscience

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Researchers have found loneliness to play a role in gene activation and to be associated with psychiatric disorders such as depression and borderline personality disorder (e.g., 1,2). For research in this area to advance, it is now time to consider why this association has been found. In my commentary I would like to raise issues to be addressed in future research on loneliness and social neuroscience.

A first issue to be addressed concerns the nature of loneliness. Researchers and theorists have made a distinction between loneliness and social isolation (3). Studies have indicated that some individuals may have large social networks and be involved in frequent social activities yet report being lonely. By contrast, other individuals may be socially isolated but not report feeling lonely. Loneliness appears to result from being dissatisfied with important aspects of relationships with others, such as the quality of the relationships or the lack of a particular type of relationship. Clearly, research needs to move beyond simply examining relationships between loneliness and the size of social networks or the frequency of social contacts.

A second issue is the "pathologization" of loneliness. Loneliness is a common experience. For example, Cutrona (4) found that 75% of freshmen students at UCLA reported feeling lonely during their first two weeks on campus. By the spring quarter of their first year, only 25% of these students reported feeling lonely. As discussed by Weiss (5), other events such as divorce or the death of a spouse can create what he described as emotional loneliness.

The research reviewed by Cacioppo et al (6) involves the effects of "chronic" loneliness (e.g., individuals who were found to be lonely over a three year period of time). It seems unlikely that loneliness experienced for a short period of time while making the transition to a new social setting (such as college) would result in such biological consequences as gene activation. At this point we do not know the necessary duration of loneliness for these consequences to occur, or whether overcoming loneliness through the formation of new or more satisfying relationships with others can prevent these negative effects of loneliness.

A similar point should be made concerning the relationship between loneliness and psychiatric disorders like depression. Developing feelings of loneliness after moving to a new social setting is unlikely to lead to the development of clinical depression. However, the inability to overcome these feelings of loneliness through the development of new relationships with others may lead individuals moving to a new setting to become depressed. Understanding how the relationship between loneliness and depression changes over time is clearly of clinical importance.

Another important issue for future research concerns whether or not chronic loneliness is the "cause" of such consequences as gene activation. Loneliness is associated with a number of other factors that could account for the associations that are described by Cacioppo et al. For example, personality characteristics such as extraversion and neuroticism are strongly related to loneliness (7); are these variables responsible for the association between loneliness and gene activation that has been found? Neuroticism may represent a "third variable" that is the cause of both loneliness and gene activation; if true, then we should find that the relationship between loneliness and gene activation becomes nonsignificant if we control for the effects of neuroticism on both of these variables. Similar issues arise concerning the relationship between loneliness and such psychiatric disorders as depression or borderline personality disorder. For example, do we find that loneliness is a predictor of developing clinical levels of depression because lonely individuals also tend to be high on neuroticism?

It is time to move beyond examining the correlation between loneliness and neurological and psychiatric outcomes to the development and testing of theoretical models of these relationships. These models need to include factors that are hypothesized to determine feelings of loneliness, such as personality characteristics and the nature of people's relationships with others. The models should in turn specify how loneliness leads to such outcomes as gene activation and the development of psychiatric disorders such as depression or personality disorders. An important issue to consider involves whether or not loneliness serves as a mediator between characteristics of the individual (e.g., personality) and their social networks and these neurological and psychiatric disorders. As K. Lewin once commented (8), there is nothing so practical as a good theory; being able to ultimately intervene and prevent these negative effects of loneliness may depend upon our ability to understand and alter its causes.

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Psychiatry and social nutritional neuroscience

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Cacioppo et al (1) elegantly outline potential contributions of social neuroscience to psychiatry. Their interdisciplinary approach could be enhanced by incorporating a nutritional perspective. Indeed, although the human brain represents only about 2% of human body mass, it accounts for ~20% of the total resting metabolic rate (2). As a consequence of the brain's intense energy requirements, metabolic aberrations can have substantial consequences for its function. In this commentary we focus on the progress and potential of social nutritional neuroscience, an area of growing interest and importance, for psychiatry.

In traditional terms, nutritional neuroscience focuses on the effects that various dietary components have on neurochemistry, neurobiology, behavior, and cognition. Social nutritional neuroscience takes a broader view that incorporates key bidirectional influences: social processes and behavior impact diet, both of which affect neurochemistry and neurobiology. These resulting dietary and biological changes may subsequently alter social and behavioral processes, ultimately creating a feedback loop. Studies addressing the dietary and biological consequences of depression help demonstrate the importance of viewing these relationships as a two-way street.

Depression can have a substantial effect on food intake. Appetite changes are a notable feature of major depressive disorder. In fact, one of the diagnostic criteria for this disorder in the DSM-5 is diet-relevant: weight gain/loss or hyperphagia/hypophagia. Depression also influences dietary preferences (3): for example, some people increase comfort food intake when depressed (4).

Depression and diet can impact the same physiological systems. Mechanistic studies have shown how depression can modulate key pathways to inflammation including sympathetic activity, oxidative stress, transcription factor nuclear factor kappa B (NF-κB) activation, and pro-inflammatory cytokine production (5). Diet affects inflammation and modifies brain function through these same processes (3,5). Both depression and stress also have well-documented negative effects on vagal activation. Because the vagus nerve innervates tissues involved in the digestion, absorption, and metabolism of nutrients, vagal activation can directly and profoundly influence metabolic responses to food, as well as inflammation, contributing to the lively interplay between the brain and the gut (5).

Diet and immune alterations may promote depression. Growing evidence suggests that people with poorer quality diets have a higher likelihood of being depressed than people with better quality diets (6). Furthermore, pro-inflammatory cytokine administration induces "sickness behaviors", i.e., behavioral changes that resemble the somatic symptoms evident in depression, like anhedonia and lethargy (7). Accordingly, depression may start a negative cascade whereby depression promotes dysregulated food consumption and physiological responses which, in turn, further enhance depression.

The bi-directional links among depression, diet, and biological responses are nicely illustrated by the relationship between depression and obesity, which is clearly linked to both diet and dysregulated physiological responses. For example, clinical depression and obesity often travel together (8). The risk for developing depression over time is 55% in obese persons, and depressed people have a 58% increased risk of becoming obese (8). In addition, a large prospective study showed that older depressed adults gained visceral fat over five years, while non-depressed adults lost visceral fat (9). Importantly, this association did not reflect changes in overall obesity, suggesting that depressive symptoms were specifically associated with changes in visceral fat, a central and important contributor to inflammation. Functioning as an endocrine organ, adipose tissue secretes a number of different peptide hormones and cytokines that influence brain function, metabolism and behavior (3).

While a poor diet increases risk for depression, a healthy diet may be protective. In a prospective study with over 10,000 participants, those who ate a Mediterranean diet that was rich in monounsaturated fats, fish, fruit, nuts, and vegetables had a lower risk for depression four years later than people who consumed diets with fewer of these foods and higher amounts of saturated fats (10). Healthy diets may also reduce anxiety symptoms, in addition to depressive symptoms (6).

After summarizing key issues in social neuroscience and its potential contribution to psychiatry, Cacioppo et al (1) concluded that neuroimaging and genetic research that focuses on specific component processes underlying social living is needed. In the field of social nutritional neuroscience, similar neuroimaging and genetic research would be valuable. In fact, an interdisciplinary approach that incorporates both social neuroscience and social nutritional neuroscience could foster unique and

provocative questions that would further our understanding of psychiatric disorders. A broader emphasis on the role of behavior as a key driver in nutritional neuroscience could also open up new vistas and prospects for future research.

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Risks of all-cause and suicide mortality in mental disorders: a meta-review

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A meta-review, or review of systematic reviews, was conducted to explore the risks of all-cause and suicide mortality in major mental disorders. A systematic search generated 407 relevant reviews, of which 20 reported mortality risks in 20 different mental disorders and included over 1.7 million patients and over a quarter of a million deaths. All disorders had an increased risk of all-cause mortality compared with the general population, and many had mortality risks larger than or comparable to heavy smoking. Those with the highest all-cause mortality ratios were substance use disorders and anorexia nervosa. These higher mortality risks translate into substantial (10-20 years) reductions in life expectancy. Borderline personality disorder, anorexia nervosa, depression and bipolar disorder had the highest suicide risks. Notable gaps were identified in the review literature, and the quality of the included reviews was typically low. The excess risks of mortality and suicide in all mental disorders justify a higher priority for the research, prevention, and treatment of the determinants of premature death in psychiatric patients.

Key words: Mortality, suicide, mental disorders, substance use disorders, anorexia nervosa, meta-review

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Higher mortality risks in many mental disorders are well recognized and may be worsening over time (1,2). Data from the Global Burden of Disease (GBD) study suggested that mental and behavioural disorders account for 8.6 million, or 0.5%, of all years of life lost to premature mortality (3). This is equivalent to 232,000 deaths in 2010, an increase from 1990, when there were 138,000 premature deaths secondary to mental disorders (4). More than three-quarters of these deaths were attributed to substance use disorders. However, substance use and mental illness are commonly comorbid and mutually amplify the risk to premature death, often by suicide.

The GBD study also reported that suicide was the 13th leading cause of death globally, and was more prevalent in regions with advanced health care systems (4). Suicide accounted for 5% of female and 6% of male deaths in persons aged 15-49 years old, and 884,000 deaths across all ages.

These stark mortality figures highlight an obvious challenge to preventive medicine, because mental disorders and substance use have evidence-based treatments. Delivering such treatments effectively should reduce the risks of premature death for individual patients, particularly from suicide.

Clarifying the pattern of risks across mental disorders is a necessary step to identify where resources can be most effectively targeted and interventions prioritized. However, syntheses of mortality risks associated with different diagnoses have not been attempted since the 1998 publication of the highly influential meta-analysis by Harris and Barraclough (5). This is despite the exponential growth in the literature over recent decades and contrasting estimates in subsequent studies for mortality in individual conditions. For example, a 2007 systematic review (1) suggested that the standardized mortality ratio (SMR) for patients with schizophrenia is 2.5, while Harris and Barraclough's estimate was 1.6. Another recent review (6) provided an SMR for opioid use of 14.7, more than twice that reported in the Harris and Barraclough review (6.4). In addition, there is now a much greater awareness of the contribution of treatable physical ill health to premature death in psychiatric patients. An understanding of the comparative data for exposure to known physical risk factors, like tobacco smoking, is also currently lacking.

With the increase in evidence over recent decades and contrasting estimates in meta-analyses, an updated review is required. This will enable clinicians to prioritize interventions based on the comparative risks of mortality across disorders, researchers to identify where gaps exist in the literature, and commissioners and policy makers to target resources more effectively. We have therefore conducted a meta-review, or a review of systematic reviews, of all-cause and suicide mortality in all major mental disorders.

METHODS

Using the Google Scholar database, a systematic search was conducted to identify systematic reviews and meta-analyses that reported on risks for all-cause and suicide mortality for unipolar depressive disorders, anxiety disorders, bipolar disorder, schizophrenia spectrum disorders, eating disorders, learning disability and autistic spectrum disorders, childhood behavioural disorders (including conduct disorder and oppositional defiant disorder), personality disorders, dementia, substance use disorders, alcohol use disorder and smoking.

We used the following search terms: 'allintitle: mortality OR death OR suicide OR suicidal OR suicidality, review OR meta-analysis OR meta-analytic, psychiatry OR psychiatric OR mental OR mood OR affective OR depression OR depressive OR dysthymia OR cyclothymia OR adjustment OR anxiety OR anxious OR "obsessive compulsive" OR

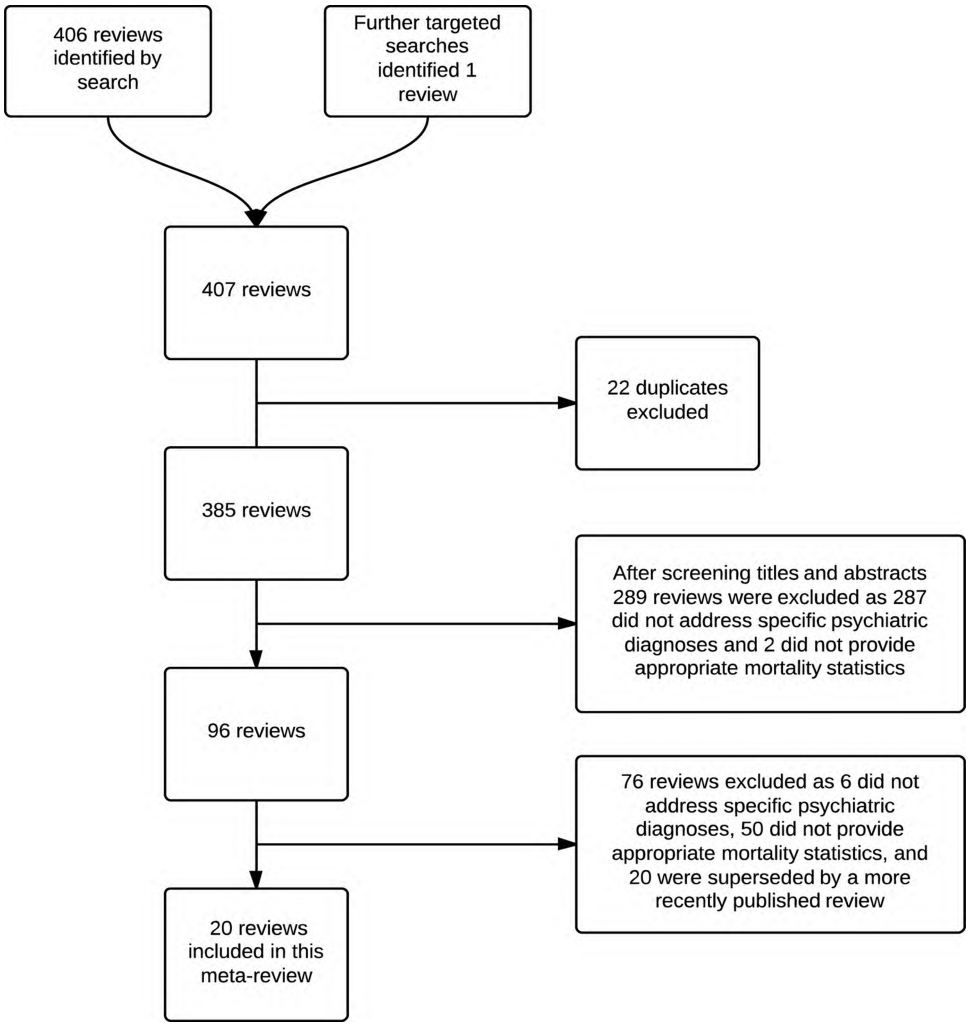

Figure 1 Flow chart of systematic search strategy

OCD OR panic OR "post-traumatic" OR posttraumatic OR PTSD OR neurosis OR neuroses OR bipolar OR manic OR schizophrenia OR psychotic OR psychosis OR psychoses OR dementia OR demented OR Alzheimer OR "learning disability" OR "learning disabilities" OR IQ OR "mental retardation" OR autism OR autistic OR Asperger OR "attention deficit" OR ADHD OR hyperactivity OR hyperkinetic OR conduct OR disruptive OR personality OR personalities OR borderline OR antisocial OR psychopathic OR dissocial OR forensic OR narcissistic OR schizoid OR schizotypal OR paranoid OR dependent OR avoidant OR "emotionally unstable" OR eating OR anorexia OR bulimia OR EDNOS OR heroin OR opioid OR opioids OR cocaine OR cannabis OR marijuana OR alcohol OR alcoholism OR benzodiazepine OR benzodiazepines OR hypnotic OR hypnotics OR amphetamine OR amphetamines OR barbiturate OR barbiturates OR smoking OR smokers OR cigarette OR cigarettes'. We targeted articles published between January 1, 1998 and February 19, 2014.

Papers were excluded if they did not report a pooled all-cause mortality or completed suicide statistic. Gender-specific estimates were reported if available. If a review was superseded by a more recently published review, only the more recent paper was included. For diagnoses where no pooled mortality statistic was found, we identified the most recent large (N>1000) single study providing data on mortality by conducting further database and citation searches.

A second search was carried out to identify systematic reviews and studies on life expectancy in mental disorders. Using the Google Scholar database, the following search terms were used: 'allintitle: review, life expectancy' and 'allintitle: life expectancy, mental OR psychiatric OR psychiatry OR mood OR depression OR bipolar OR schizophrenia OR personality OR anxiety OR smoking OR substance OR opioid OR alcohol OR anorexia OR eating'. We targeted articles published between January 1, 1998 and February 19, 2014. Supplementary citation searches were used to identify additional studies.

Table 1 All-cause and suicide mortality in mental disorders

Diagnosis	All-cause mortality risk estimate (95% CI)	Statistic	Men (95% CI)	Women (95% CI)	Suicide risk estimate (95% CI)	Statistic	Men (95% CI)	Women (95% CI)	AMSTAR score
Opioid use (6,14)	14.7 (12.8-16.5)	SMR			13.5 (10.5-17.2)	SMR	7.6 (4.4-12.1)	3.6 (0.1-19.9)	7, 1
Amphetamine use (15)	6.2 (4.6-8.3)	SMR*	5.9 (4.1-8.1)	7.8 (3.9-14.0)					8
Cocaine use (16)	4 to 8	SMRs							7
Anorexia nervosa (17,18)	5.9 (4.2-8.3)	SMR				SMR*		31.0 (21.0-44.0)	2, 3
Alcohol use disorder (19,20)	4.6 (2.7-7.7)	RR	3.4 (3.0-3.8)	4.6 (3.9-5.4)		SMR	8.8 (6.4-12.1)	16.4 (10.7-25.2)	5, 5
Autism spectrum disorder (21)	2.8 (1.8-4.2)	SMR	2.1 (1.7-2.7)	7.2 (3.0-17.2)					7
Heavy smoking (22)		**RR - WA**	**2.4**	**2.7**					**2**
Schizophrenia (1)	2.5 (2.2-2.4)	SMR	3.0	2.4	12.9 (0.7-174.3)**	SMR*			6
Dementia (23)	1.5 to 3.0	RRs							5
Moderate smoking (22,24)		RR -WA	2.0	2.0	1.8 (1.5-2.2)	RR	1.7 (1.4-2.1)	1.8 (1.2-2.7)	2, 6
Bulimia nervosa (17,18)	1.9 (1.4-2.6)	SMR				SMR*		7.5 (1.6-11.6)	2, 3
Eating disorder NOS (17)	1.9 (1.5-2.5)	SMR							2
Depression (25,26)	1.6 (1.6-1.7)	RR			19.7 (12.2-32.0)	SMR			7, 3
Depression in the elderly (27)	1.6 (1.4-1.8)	RR							4
Dysthymic disorder (27)	1.4 (0.9-2.0)	RR							4
Cannabis use (28)		RRs	1.2 to 1.3	1.1 (0.8-1.5)					4
Borderline personality disorder (29)					45.1 (29.0-61.3)	SMR*			1
Bipolar disorder (26)					17.1 (9.8-29.5)	SMR			3
Personality disorders (30)						RR	4.1 (3.0-5.8)	1.8 (0.7-5.2)	3
Anxiety disorder (any type) (31)					3.3 (2.1-5.3)	OR			7
Post-traumatic stress disorder (31)					2.5 (0.5-13.4)	OR			7

SMR – standardized mortality ratio, OR – odds ratio, RR – relative risk, WA – weighted average, AMSTAR – Assessing the Methodological Quality of Systematic Reviews, NOS – not otherwise specified
*Not adjusted for random effects, **90% confidence intervals

Table 2 Single studies providing data on mortality risks in disorders where systematic reviews were not identified

Diagnosis	Statistic	All-cause mortality risk estimate (95% CI)	Men	Women
Early-onset dementia (32)	HR	43.3 (3.1-600.4)		
Post-partum psychiatric admission (at 1 year) (33)	SMR			19.5 (11.7-30.4)
Disruptive behaviour disorder* (34)	SMR		5.8 (4.1-8.0)	4.1 (1.3-9.4)
Methamphetamine use (35)	SMR	4.7 (4.5-4.8)	4.9 (4.7-5.0)	4.4 (4.1-4.6)
Acute and transient psychotic disorder (36)	SMR	4.7 (4.1-5.3)	4.9 (4.2-5.8)	4.4 (3.6-5.4)
Personality disorder (37)	SMR	4.2 (3.0-5.6)	3.5 (2.2-5.5)	5.0 (3.2-7.5)
Late-onset dementia (32)	aHR	3.3 (1.8-6.2)		
Schizophrenia in the elderly (38)	SMR	2.7 (2.6-2.8)	3.0 (2.9-3.1)	2.6 (2.5-2.6)
Intellectual disability (moderate to profound) (39)	SMR	2.8 (2.5-3.0)	2.3 (2.0-2.6)	3.2 (2.8-3.7)
Bipolar disorder (40)	aHR		2.0 (1.9-2.2)	2.3 (2.2-2.5)
Adults with childhood ADHD (41)	SMR	1.9 (0.8-4.3)		
Comorbid anxiety/depression (42)	OR	1.4 (1.2-1.7)	1.4 (1.1-1.8)	1.5 (1.2-1.8)

SMR – standardized mortality ratio, HR – hazard ratio, aHR – adjusted hazard ratio, OR – odds ratio, ADHD – attention-deficit/hyperactivity disorder
*Mainly consists of conduct disorder and oppositional defiant disorder

The majority of reviews reported SMRs. An SMR compares the gender and age standardized mortality of a sample (i.e., people with a mental disorder) to the whole population. Some studies instead reported relative risks (RRs) or odds ratios (ORs). A RR is defined by the incidence in the exposed divided by the incidence in the unexposed. The OR is defined by odds of an event (i.e., death or suicide) in the exposed divided by the odds of such an event in the unexposed (7). The OR and RR tend to report a larger effect than SMR, because the denominator in the SMR includes those with mental illness (whereas these individuals are excluded in the denominator for an OR or RR). Typically, the OR is similar to the RR when events are rare, as is the case for death and suicide (8).

One of the authors (EC) extracted mortality statistics with their 95% confidence intervals. Another researcher re-assessed the data extraction – no discrepancies were identified. If reported, RRs/ORs adjusted by age and gender were included. We chose random effects estimates if reported, as heterogeneity in individual reviews was high.

Each review was rated using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) (9), an empirically developed scoring system to assess the quality of systematic reviews, made up of the following eleven criteria scored from 0 to 1: Was an "a priori" design provided? Was there duplicate study selection and data extraction? Was a comprehensive literature search performed? Was the status of publication (i.e., grey literature) used as an inclusion criterion? Was a list of studies (included and excluded) provided? Were the characteristics of the included studies provided? Was the scientific quality of the included studies assessed and documented? Was the scientific quality of the included studies used appropriately in formulating conclusions? Were the methods used to combine the findings of studies appropriate? Was the likelihood of publication bias assessed? Was the conflict of interest stated? Scores of 0 to 3 are considered low, 4 to 7 medium, and 8 to 11 high (10).

We excluded a review of mortality in benzodiazepine use (11) as it only provided risk data for prescribed use, not misuse. In addition, a review of suicide in bipolar disorder (12) was excluded as it did not provide a pooled mortality statistic. Finally, a review of suicide in attention-deficit/hyperactivity disorder (ADHD) (13) was excluded as it did not use comparative population data.

RESULTS

The search for reviews on all-cause mortality identified 406 citations, and additional citation searches identified one review. After removing duplicates, and screening titles and abstracts, 96 reviews were identified. After exclusions, a final sample of 20 systematic reviews and meta-analyses (1,6,14-31) were included (Figure 1, Table 1). Excluding the smoking review, these reviews included over 1.7 million individuals with mental disorders and investigated over a quarter of a million deaths. We identified a further 12 mortality estimates from the largest single studies for disorders where there were no systematic reviews (32-42) (Table 2).

The search for reviews on life expectancy yielded 28 papers, none of which was relevant. The second search, for single studies, identified 123 relevant papers, of which 8 were included. Further citation searches, and the results from the above all-cause and suicide mortality search, identified one further systematic review and five relevant

Table 3 Single studies and reviews reporting life expectancy in mental disorders

Diagnosis	Years lost	Men (95% CI)	Women (95% CI)	Population
Depressive episode/recurrent depressive disorder (43)		10.6 (9.5-12.8)	7.2 (6.3-8.1)	UK
Affective disorders (44)		15.6 to 17.4	11.1 to 13.6	Denmark, Finland and Sweden
Bipolar disorder (43)		10.1 (8.9-11.3)	11.2 (10.2-12.1)	UK
Bipolar disorder (45)		13.6 (13.2-14.0)	12.1 (11.8-12.4)	Denmark
Bipolar disorder (46)		9.0	9.0	Israel
Bipolar disorder (40)		8.5	9.0	Sweden
Bipolar disorder (47)		12.7 to 19.8	11.0 to 16.2	Denmark, Finland and Sweden
Schizoaffective disorder (43)		8.0 (6.9-9.1)	17.5 (14.4-20.7)	UK
Schizophrenia spectrum (44)		15.5 to 20.1	10.9 to 17.3	Denmark, Finland and Sweden
Schizophrenia (43)		14.6 (12.3-15.8)	9.8 (8.9-10.7)	UK
Schizophrenia (45)		18.7 (18.4-19.0)	16.3 (16.2-16.8)	Denmark
Schizophrenia (46)		11.0	13.0	Israel
Schizophrenia (48)	14.7	15.3	11.4	Denmark
Schizophrenia (47)		17.1 to 20.0	15.6 to 16.9	Denmark, Finland and Sweden
Schizophrenia (49)		15.0	12.0	Sweden
Personality disorders (44)		13.0 to 21.9	14.5 to 20.0	Denmark, Finland and Sweden
Personality disorders (37)		17.7 (15.9-19.5)	18.7 (17.3-20.1)	UK
Younger onset dementia (50)	9.6 to 19.4			Review (1985-2010)
Late onset dementia (50)	1.3 to 9.2			Review (1985-2010)
Alzheimer's dementia (50)	0.9 to 16.7			Review (1985-2010)
Fronto-temporal dementia (50)	11.5 to 15.4			Review (1985-2010)
Dementia (50)		0.4 to 11.4	1.4 to 15.3	Review (1985-2010)
Alcohol use (51)		17.1 (15.4-18.8)	10.8 (9.6-12.1)	UK
Opioid use (51)		9.0 (7.8-10.2)	17.3 (15.4-19.2)	UK
Substance use disorders (43)		13.6 (12.5-14.8)	14.8 (13.4-16.2)	UK
Substance abuse (44)		21.3 to 23.6	17.6 to 22.6	Denmark, Finland and Sweden
Heavy smoking (52)		9.2	9.4	Denmark
Smoking (53)		8.0	10.0	Japan
Smoking (54)		**8.7 (7.6-9.6)**	**7.6 (6.3-8.9)**	**USA**

primary studies. Therefore, we identified 14 relevant publications (37,40,43-54) (Table 3).

All mental disorders had higher mortality risks than general population samples, but there was a considerable range from dysthymia, with an RR of 1.4, to opiate use disorders, with an SMR of 14.7. Substance use disorders and anorexia nervosa had the highest mortality risks (Table 1). For schizophrenia and autism, mortality risks were at least as high as heavy smoking (Table 4).

The pattern of suicide estimates was different from all-cause mortality (Table 1). Borderline personality disorder, depression, bipolar disorder, opioid use and schizophrenia, as well as anorexia nervosa and alcohol use disorder in women, had higher suicide risks than most other disorders. A sample of anorexic patients presenting to specialist care (outpatients and inpatients) was an outlier for suicide (SMR=31.0, 95% CI: 21.0-44.0) (18). As a review on suicide in borderline personality disorder (29) did not provide a pooled mortality statistic, we combined data to provide a median SMR (SMR=45.1, 95% CI: 29.0-61.3). Again, these patients were mostly hospitalized and thus represent the severe end of the diagnostic spectrum.

Two reviews (23,27) reported data on all-cause mortality relevant to older adults. Increases were seen in depression

Table 4 Mortality risk in specific mental disorders compared to heavy smoking

Diagnosis	All-cause mortality (risk compared with the general population)	Prevalence ratio (risk compared with that for heavy smoking)
Post-partum psychiatric admission (at 1 year) (33)	19.5	7.7
Opioid use (6)	14.7	5.8
Amphetamine use (15)	6.2	2.4
Cocaine use (16)	6.0**	2.4
Anorexia nervosa (17)	5.9	2.3
Disruptive behaviour disorder* (34)	5.0***	1.9
Methamphetamine use (35)	4.7	1.8
Acute and transient psychotic disorder (36)	4.7	1.8
Alcohol use disorder (19)	4.6	1.8
Personality disorder (37)	4.2	1.7
Intellectual disability (moderate to profound) (39)	2.8	1.1
Heavy smoking (22)	**2.6****	**1.0**
Schizophrenia (1)	2.5	1.0
Bipolar disorder (40)	2.2**	0.8
Bulimia nervosa (17)	1.9	0.8
Eating disorder NOS (17)	1.9	0.8
Adults with childhood ADHD (41)	1.9	0.8
Depression (25)	1.6	0.6
Dysthymic disorder (27)	1.4	0.6
Comorbid anxiety/ depression (42)	1.4	0.6
Cannabis use (28)	1.2**,***	0.5

ADHD – attention-deficit/hyperactivity disorder, NOS – not otherwise specified *Mainly consists of conduct disorder and oppositional defiant disorder, **mid-point of range, ***mean value of male and female mortality

(RR=1.6, 95% CI: 1.4-1.8), and dementia (RRs of 1.5 to 3.0). These are not dissimilar to risks of death for elderly smokers (RR=1.8, 95% CI: 1.7-2.0) (55).

The reduction in life expectancy associated with moderate to heavy smoking ranged from 8 to 10 years. This range is similar to that reported for a single depressive episode or recurrent depressive disorder (7-11 years), but lower than that associated with substance use (9-24 years), personality disorders (13-22 years), schizophrenia (10-20 years), and bipolar disorder (9-20 years) (Table 3).

We did not identify any reviews on all-cause mortality for some major diagnostic classes, including bipolar disorder, anxiety disorders, personality disorders, ADHD, obsessive-compulsive disorder and post-traumatic stress disorder. For suicide, we did not identify systematic reviews for cocaine and amphetamine use, autism, dementia and ADHD. In addition, we identified no reviews of mortality in people with dual diagnosis.

DISCUSSION

To our knowledge, this is the first meta-review of all-cause mortality and suicide risks in mental disorders. We identified 20 systematic reviews and meta-analyses that reported such risks in over 1.7 million individuals with mental disorders and over a quarter of a million deaths. We located a further 14 publications on life expectancy.

We found that all the reported mental disorders had elevated all-cause mortality risks compared with the general population. Several disorders had higher or equal mortality risks compared to heavy smoking. However, there was considerable variation between diagnoses, for both mortality and completed suicide. Substance use disorders and anorexia nervosa had the highest mortality ratios. The mortality data for schizophrenia (SMR=2.5) and bipolar disorder (adjusted hazard ratio=2.0-2.3) were comparable with that for heavy smoking (RR=2.4-2.7). This result was underscored by the data for life expectancy, where all major mental disorder diagnoses had reductions (7-24 years) similar to, or greater than, heavy smoking (8-10 years).

For suicide mortality, borderline personality disorder, depression, bipolar disorder, opioid use and schizophrenia, as well as anorexia nervosa and alcohol use disorder in women, had substantially increased rates (greater then 10 times) compared with the general population. There was also an increased risk for suicide in moderate smokers, but this was lower than the mental disorder diagnoses investigated.

A limitation of this meta-review is the varied quality of the reviews (7 out of 20 had a low AMSTAR quality rating score, a further 12 had a medium score, and only one review could be considered of a high quality). Common omissions in the reviews were lack of testing for publication bias, not searching grey literature, and not having two data extractors. An additional limitation is the underreporting of suicide statistics which is common in some countries (56) and the potential contribution of psychiatric comorbidity to mortality.

Few reviews specified or commented on the samples included in their meta-analyses. The common use of solely inpatient data may overestimate risks for disorders mild enough to be managed in primary care (57). This may not be the case for schizophrenia, in which mortality was compared between inpatient and outpatient populations and no difference was found (1). Furthermore, the review on depression (25) had similar mortality risks for all patients compared with depressed persons identified solely using community based data. The reviews on dysthymia and depression in the elderly (27) and dementia (23) also used community and outpatient clinic data only. On the other hand, the review on

amphetamine use only reported one SMR, which was taken from an inpatient sample (15). Furthermore, the two outliers for suicide risk – anorexia nervosa (18) and borderline personality disorder (29) – were taken from samples with high proportions of inpatients, and thus represent the most severe cases of these disorders.

Most of the primary studies making up the reviews made use of large administrative data sets. As recently highlighted by Ioannidis (58), these data sets have their weaknesses, despite the precision associated with their large sample sizes. Analyses using such data are typically overpowered, so that statistically significant results can be obtained despite very small differences in mortality. As a result, it is not only the statistical significance that is important, but the size of the difference in mortality risk needs to be considered and balanced against the relative risk. Further, data were not collected for research purposes and hence diagnoses may be subject to substantial noise. Sensitivity analysis should be undertaken to examine diagnoses that have been made in different ways and also the degree of miscoding. Lack of, and error in the measurement of covariates may lead to inadequate adjustment, as can differences in the coding and treatment between hospitals and other health care settings (23).

Smoking has been an important target for prevention because it is so common and perceived to be so dangerous. Mental disorders are also relatively common when considered together, but the risk to life is not perceived in the same way. From a public health perspective, patients with serious mental illness should be designated as a high risk population for physical illness, given the substantial health disparities compared with the general population. National strategies could and should target improving access to physical health care (59).

In conclusion, the impact on mortality and suicide of mental disorders is substantial, and probably poorly appreciated as a public health problem. The scale of the unmet needs complements the social burden and costs of mental disorders (60). These findings must justify a higher priority for research, prevention and treatment of the determinants of premature death in psychiatric patients.

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Effectiveness of programs for reducing the stigma associated with mental disorders. A meta-analysis of randomized controlled trials

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The stigma associated with mental disorders is a global public health problem. Programs to combat it must be informed by the best available evidence. To this end, a meta-analysis was undertaken to investigate the effectiveness of existing programs. A systematic search of PubMed, PsycINFO and Cochrane databases yielded 34 relevant papers, comprising 33 randomized controlled trials. Twenty-seven papers (26 trials) contained data that could be incorporated into a quantitative analysis. Of these trials, 19 targeted personal stigma or social distance (6,318 participants), six addressed perceived stigma (3,042 participants) and three self-stigma (238 participants). Interventions targeting personal stigma or social distance yielded small but significant reductions in stigma across all mental disorders combined (d=0.28, 95% CI: 0.17-0.39, p<0.001) as well as for depression (d=0.36, 95% CI: 0.10-0.60, p<0.01), psychosis (d=0.20, 95% CI: 0.06-0.34, p<0.01) and generic mental illness (d=0.30, 95% CI: 0.10-0.50, p<0.01). Educational interventions were effective in reducing personal stigma (d=0.33, 95% CI: 0.19-0.42, p<0.001) as were interventions incorporating consumer contact (d=0.47, 95% CI: 0.17-0.78, p<0.001), although there were insufficient studies to demonstrate an effect for consumer contact alone. Internet programs were at least as effective in reducing personal stigma as face-to-face delivery. There was no evidence that stigma interventions were effective in reducing perceived or self-stigma. In conclusion, there is an evidence base to inform the roll out of programs for improving personal stigma among members of the community. However, there is a need to investigate methods for improving the effectiveness of these programs and to develop interventions that are effective in reducing perceived and internalized stigma.

Key words: Stigma, social distance, depression, schizophrenia, mental illness, personal stigma, perceived stigma, self-stigma, educational interventions, consumer contact, Internet programs

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Stigmatizing attitudes to mental disorders are responsible for substantial distress, a reluctance to seek appropriate help (1,2), and reduced employment, social and accommodation opportunities among people with a mental illness (2,3). Moreover, stigma is not confined to any particular mental disorder, but rather is directed to a range of mental illnesses, such as schizophrenia, mood disorders, anxiety disorders and eating disorders (e.g., 4-8).

There is increasing acknowledgement among governments and policy makers of the importance of stigma as a public health problem and the need to implement strategies for addressing it (e.g., 9-11). Stigma is also the focus of global strategies: the World Health Organization has called for action amongst its member nations to reduce stigma (12), and several activities in this area have been implemented by the WPA (e.g., 13).

Given the importance of these interventions to mental health consumers and their cost to governments, it is vital that the roll out of stigma programs is informed by high quality research evidence. Ideally, such evidence should be collected and synthesized using a systematic approach.

To date there have been two quantitative systematic reviews of the effectiveness of stigma reduction interventions (14,15).

The first review focused on interventions designed to decrease the stigmatizing attitudes of members of the community towards people with a mental illness (14). This type of stigma has been variously described as public or personal stigma (an individual's own attitude towards people with a mental illness). Based on uncontrolled and controlled trials published prior to October 2010, the reviewers concluded that consumer contact and educational interventions were effective in reducing the public stigma associated with mental illness. They also reported that contact interventions were more effective than educational interventions for an adult population, while the converse was true for young people.

There were some limitations of this review. First, it is apparent that the authors used multiple effect sizes from a study as separate entries rather than combining them or entering only one effect size. Second, the authors did not investigate the possibility of different findings depending on the type of mental disorder investigated, nor provide descriptive information about the distribution of different conditions. Finally, the paper limited the interventions types to protest, contact and education, and included only studies and outcomes which focused on the individual's personal views about stigma. Other types of stigma, including the individual's beliefs about the attitudes of others to mental illness ("perceived stigma") and the negative attitudes of an individual to his/her own mental illness ("self-stigma" or "internalized stigma"), were not investigated.

The second review investigated the effectiveness of "mass media" interventions in reducing discrimination and negative community attitudes and emotions with respect to people

with a mental illness (15). The review included relevant randomized controlled trials and interrupted time series studies published up until August 2011. The authors concluded that the interventions had a small to moderate effect on stigma. Again, the authors did not investigate the effect of different disorders separately. In addition, the review apparently pooled outcome data for personal attitudes to mental disorders (public stigma) with those reporting perceived stigma in the community.

To date there have been no quantitative reviews of interventions aimed to reduce the internalized stigma associated with a person's own mental illness (self-stigma). A recent non-quantitative systematic review has been published (16), but a consideration of the individual studies in the review suggests that they were not confined to self-stigma. In particular, over half of the studies measured perceived rather than self-stigma (16). In addition, at least one of the studies measured the individuals' personal attitudes to mental illness (or "public stigma") rather than their attitude to their own mental health symptoms (17).

The purpose of the present study was to undertake a quantitative analysis to determine the effectiveness of different types of interventions (e.g., education, consumer contact, cognitive behavior therapy) in reducing different types of stigma (personal, perceived and internalized) for different types of mental disorder.

METHODS

Search methodology

Three databases (PubMed, PsycINFO and Cochrane) were searched for potentially relevant abstracts published prior to November 2012. The search was undertaken at three time points: November 2008, December 2009 and November 2012.

The search terms for the study were developed by conducting a preliminary search of PubMed using the terms "stigma" AND "mental illness" and identifying key terms used in a series of the returned papers. The mental illness concept was expanded into the search terms "mental illness", "mental disorders" OR "mental*" OR "mental health" OR "mood" OR "affective" OR "mind" OR "psychological distress", OR "psychol*" OR "psychopatholog*" OR "psychiatr*" OR "emotional*" OR "attitude to health" OR "education" OR "eating disorder" OR "substance us*" OR "substance abus*". The stigma concept was expanded to incorporate the search terms "stigma*" OR "discriminat*" OR "antistigma" or "anti-stigma" or "stigma change" OR "stigma reduction" or "stereotyp*" OR "prejudice" OR "social distance". In all cases the search domain was limited to "humans" and "controlled clinical trials" OR "randomized controlled trials".

To ensure that all studies relevant to depression, anxiety and bipolar disorder were captured in the search methodology, additional searches were undertaken for the period prior to November 2012 using the following specific terms: "depression" OR "depressed" OR "depressive" OR "dysthymia" OR "dysthymic" OR "postnatal depression" OR "PND" or "seasonal affective disorder" OR "SAD"; "anxiety" OR "panic" OR "agoraphobi*" OR "social phobia" OR "generalized anxiety disorder" OR "GAD" OR "obsessive compulsive" OR "OCD" OR "adjustment disorder" OR "separation anxiety" OR "post-traumatic stress" OR "PTSD" OR "phobi*" OR "social anxiety"; "manic" OR "mania" OR "hypomania*" OR "cyclothymi*" OR "bipolar".

Study identification

Potentially relevant studies were identified using a multi-step process (see Figure 1). A total of 8,246 records were retrieved from the primary key word search. Of these, 2,165 duplicates across databases (and across small overlapping time periods for the three searches) were removed, leaving a total of 6,081 abstracts (Stage 1). The titles and if necessary the abstracts were then screened by two raters to remove any study that did not mention in the title (or in the abstract if the title was ambiguous) stigma and mental illness or synonyms thereof (Stage 2). The remaining abstracts (N=763) were coded by one rater and checked by a second as either relevant/potentially relevant or not relevant according to a number of exclusion criteria. Studies were excluded if they: did not explicitly report change in stigma; failed to report stigma data; reported the correlates of stigma but not the effect of interventions to reduce stigma; included participants diagnosed with a comorbid physical condition (e.g., cancer); were concerned only with scale development or measurement; addressed the stigma associated with factors other than mental illness such as race, religion, physical disability; or involved a carer or parent survey in which the respondents answered on behalf of the person in their care. Discrepancies between raters were resolved by discussion.

Following the exclusion of irrelevant abstracts (Stage 3), 154 papers remained and were retrieved for further consideration by one author and checked by a second. Papers that satisfied one or more of the exclusion criteria were removed, as were seven non-English articles and one conference report, yielding a total of 96 relevant papers (Stage 4). The non-English papers were excluded for pragmatic reasons (cost of translation). Based on the English abstract and table content, only two of these non-English papers were rated as of probable or definite relevance (18,19). Of the retrieved papers, 34 reported findings from 33 distinct randomized controlled trials.

The search aiming to identify papers focused specifically on depression, anxiety or bipolar disorder returned 344, 315, and 38 abstracts, respectively, but did not result in the identification of any additional relevant studies. The systematic review was then conducted on the above retrieved 34 papers (17,20-52).

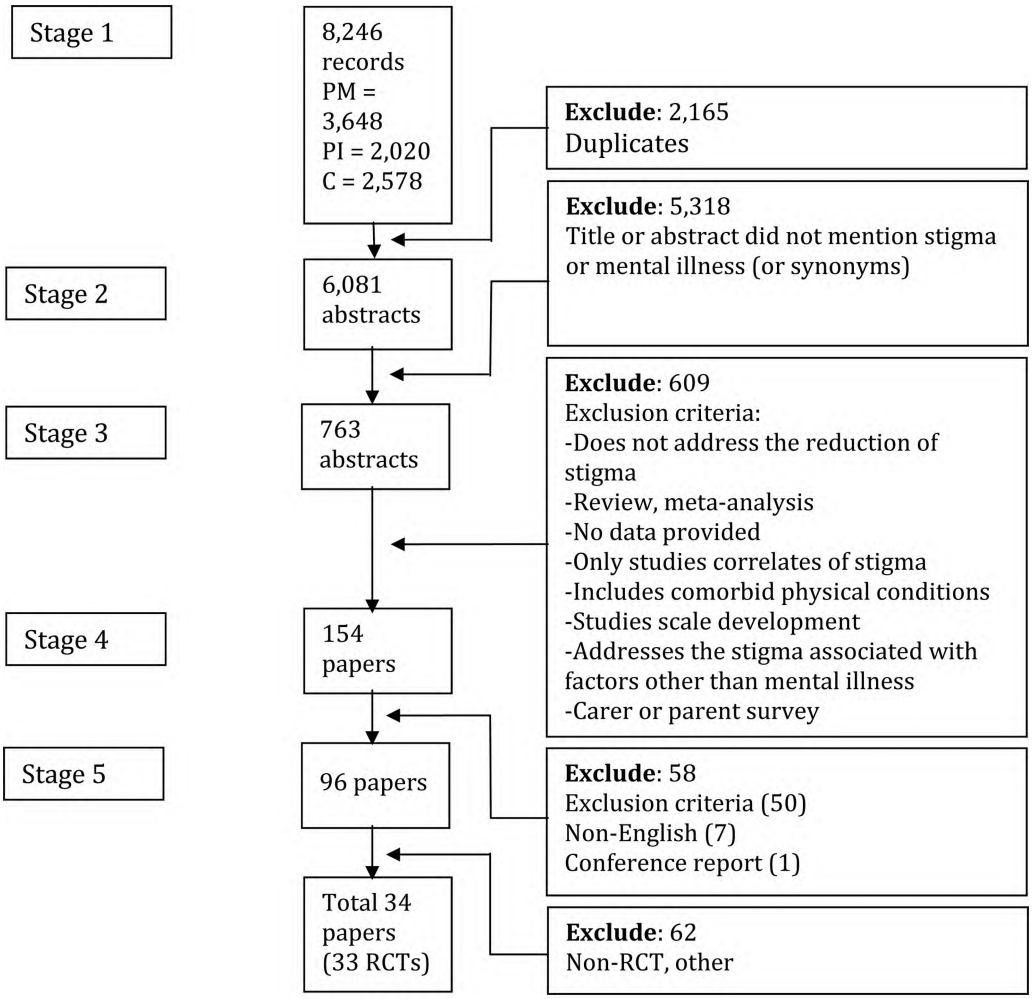

Figure 1 Study identification flow diagram. PM – PubMed, PI – PsycINFO, C – Cochrane, RCT – randomized controlled trial

Coding of included papers

Each relevant paper was independently coded by two raters, with discrepancies resolved by subsequent discussion. Each study was coded using a proforma sheet for intervention, participant and study design characteristics, and stigma outcome measures.

The coded intervention characteristics included the general type of intervention (education, consumer contact, protest, other); the delivery method (online, individual, group, distribution of material, other), and the mental health problems targeted by the intervention (e.g., depression, anxiety, psychosis, substance abuse, "mental illness"). Each intervention in a study was also rated according to whether it yielded a statistically significant positive outcome. The coded participant characteristics were age, gender, and whether the sample constituted a specific social and/or cultural group. The coded study characteristics included country in which the intervention took place, sample size, number of conditions, method of recruitment, point of intervention (universal, indicated, diagnosed), length of the longest follow-up, whether the study employed an intent-to-treat (ITT) analysis (yes, no), and whether the study was affected by performance, detection and/or selection bias (53).

In each study, the stigma outcome measures were coded for the mental health problem or disorder to which it referred, and the type of stigma assessed (personal/public, social distance, perceived, self/internalized, discrimination, and other). Personal stigma referred to the respondent's personal attitudes to people with a mental disorder (e.g., "People with depression should snap out it") or their emotional responses to them (e.g., fear). Social distance referred to the willingness of a person to make contact socially with a person with a mental illness (e.g., to live next door to a person with depression). Perceived stigma referred to the respondent's belief about the attitudes of others to people with a mental disorder (e.g., "Most people believe that people with depression should snap out of it"). Self- or internalized stigma was concerned with a person's belief or anticipated belief about his/her own mental disorder (e.g., "I

think I should snap out of my depression"). Discrimination referred to negative behaviors (e.g., sitting further away from a person with a mental illness).

Finally, coders recorded whether the study was qualitative or quantitative and whether the outcomes were statistically significant in the expected direction.

Analyses

Meta-analyses were undertaken using the Comprehensive Meta Analysis Software program (CMA; Version 2.2.064) (54) and a random effects model. The latter was selected because it was anticipated that there would be true heterogeneity in effect sizes due to the variation in participant, intervention and outcome measure characteristics. Wherever possible, between group effect sizes (standardized mean difference) were computed from post-test data provided in the article, including group mean and standard deviations or frequencies in the case of dichotomous data. In the absence of simple post-test data, effect sizes for two studies were computed from the time-condition interaction effects (25,39) and a between effect size for a third study (20) was calculated from the pre-post gain scores and their standard deviations for each condition. The effect sizes for clustered randomized controlled trials were calculated using the approximation method outlined in the Cochrane Handbook of Systematic Reviews (55). Within a study, using the CMA program, effect sizes were combined across stigma measures, types of mental illness and interventions, such that only one data point per study was incorporated in each meta-analysis. Interventions which were not intended to reduce stigma (29,37) were not included in the combined value.

Separate meta-analyses were undertaken for personal stigma (including social distance) and perceived stigma, considering all studies for which effect sizes could be estimated. In addition, meta-analyses were undertaken for subsets of the above (e.g., all educational interventions targeting personal stigma associated with depression), where there were at least two studies in a subset (see 56).

For each meta-analysis, the Q and I^2 statistic was computed, and the latter employed as an indicator of the degree of heterogeneity between studies, using the criteria employed by Higgins and Green (55). Measures of publications bias were inspected using funnel plots, the Duval and Tweedie trim and fill procedure (57) and Egger's test (54).

RESULTS

Study characteristics

Of the 33 identified trials, a substantial minority employed more than one type of stigma outcome (N=11) and several targeted stigma associated with more than one mental disorder or problem (N=4).

With respect to stigma type, the greatest research focus was on personal/public stigma, followed by perceived stigma, with few studies targeting self-stigma outcomes. In particular, 18 studies reported one or more personal/public stigma outcomes, of which seven were concerned with mental illness/psychological distress, seven with depression, five with psychotic disorders, one with generalized anxiety, one with postnatal depression and one with substance abuse. Ten studies reported social distance outcomes (mental illness, N=3; psychosis, N=3; depression, N=3; substance abuse, N=1; schizophrenia and depression (undifferentiated), N=1). Eight studies reported perceived stigma outcomes (depression, N=4; mental illness, N=2; psychosis, N=2; bipolar disorder, N=1). Three studies reported self-stigma outcomes (general mental illness, N=2; psychotic disorder, N=1).

A further six studies focused on stigma associated with help-seeking for general mental illness/psychological issues (N=5) and depression (N=1). Five studies reported findings for scales comprising a mixture of different types of stigma (30,31,36,40,50), with one incorporating a substantial percentage of non-mental health stigma items (31). Finally, the composition of items in the stigma scale of one study was unclear based on the references supplied, but was apparently primarily focused on the perceived stigma of help-seeking (26).

The most common type of intervention involved education. All but three of the 18 trials targeting personal/public stigma incorporated at least one arm either comprising education alone (N=12) or education in combination with another type of intervention (N=3). Similarly, eight of the ten studies of social distance employed education in at least one arm, and all but one of the eight perceived stigma studies incorporated education either alone or in combination.

The next most common intervention was consumer contact. Six of the 18 studies of personal stigma and four of the 10 studies of social distance employed an intervention involving consumer contact at least in part. Consumer contact was not common in the perceived stigma studies (one study combined with education) or the self-stigma studies (one study combined with cognitive restructuring).

Other interventions included cognitive behavior therapy/cognitive restructuring, acceptance and commitment therapy, mindfulness, narrative enhancement, motivational interviewing, trauma risk management, simulation of hallucinations, public service message, tailored feedback, and help-seeking resources.

Of the 33 trials, 10 employed an online medium for intervention delivery, two a computer-based medium not incorporating the Internet, 18 a face-to-face group approach, and three distribution of hard-copy educational material. Four of the studies delivered the intervention in the form of a video alone. Two studies delivered interventions via the telephone, and one study used an audio recording as an intervention.

Interventions ranged in length from 1 minute to 20 hours and from 1 to 20 modules or sessions. The distribution of the

intervention durations was bimodal, with the most common lengths being 15 minutes and 1 hour. The median and mean intervention durations were 1 and 3.7 hours, respectively.

Targeted groups included, in order of frequency, tertiary students (N=12 studies), consumers (N=5), school students (N=3), members of the defence forces (N=3), members of the general community (N=3), workplace employees (N=2), teachers (N=1), general health professionals (N=1), mental health professionals (N=1), rural population (N=1), people from a non-English speaking background (N=1) and elite athletes (N=1). The majority of the studies recruited participants via tertiary institutions (N=12) or mental health services (N=8), with the remainder being recruited by means of direct contact via professional groups (N=4), schools (N=3), the military (N=3), general advertising (N=3), and the electoral roll (N=1).

The mean age of the samples in the studies ranged from 14.7 to 65.4 years. All studies recruited both men and women, but 17 were comprised of more than 65% females and five of more than 65% males. The majority of studies were undertaken in the United States (N=18) or Australia (N=9), with two studies conducted in the UK, and one each in Hong Kong, Finland, Russia and Turkey.

Between 39 and 2,259 participants were randomized into the control or intervention conditions of each study. The majority of studies incorporated only one intervention condition (N=21), while eight employed two intervention conditions, and four used more than two interventions. The majority of control conditions involved an attention control (N=14 studies), with five and four other studies employing treatment as usual or a wait-list control, respectively. Ten of the control groups did not involve any activity. Of the 33 studies, 20 (61%) incorporated a follow-up assessment, of which six (18%) entailed follow-up periods of at least 6 months.

Five studies had no attrition. Of the remaining 28 studies, 15 employed an intent-to-treat (ITT) analysis. Eighteen of the 33 studies were affected by performance bias, 11 by attrition bias, two by selection bias and one by detection bias.

Meta-analyses

Twenty-seven of the 33 studies reported data that could be incorporated into a meta-analysis. Table 1 contains a summary of these studies, grouped by type of stigma and subcategorized according to the condition targeted by the stigma measure. The results of quantitative meta-analyses are reported separately for personal stigma/social distance (6,318 participants), perceived stigma (3,042 participants) and self-stigma (238 participants).

None of the six studies focusing on help-seeking associated with mental illness was included in the meta-analyses, because three of them contained data that were not amenable to the purpose (26,36,40), one comprised a high percentage of non-mental illness stigma items (31), and four used a stigma scale incorporating a mixture of different stigma types (30,36,40,50).

Personal stigma

Overall, 19 of the 23 studies evaluating the effect of interventions on personal stigma or social distance or both generated data from which it was possible to compare the effect of an intervention vs. a control condition (17,21,23-25,32, 33,37-39,41,42,47,48,50-52). The remaining four studies either did not provide sufficient data to compute a suitable effect size (22,28), or contained insufficient detail to determine the direction of the effect (36) or confidently interpret the data provided (45).

The outcome of the meta-analysis of the personal stigma studies is summarized in Table 2, separately for all mental health conditions (N=19 studies), depression (N=8), generic mental illness/mental health problems (N=6) and psychosis/schizophrenia (N=6).

Overall, the interventions were effective in reducing personal stigma. The forest plot is depicted in Figure 2. The pooled mean effect size across all conditions and interventions was small (d=0.28, 95% CI: 0.17-0.39), but statistically significant ($p<0.001$). There was a moderately significant level of heterogeneity across studies, which disappeared when an outlier study (41) was removed. The pooled mean effect size remained statistically significant after removal of the outlier (d=0.22, 95% CI: 0.14-0.29, $p<0.001$).

A similarly significant pooled effect and heterogeneity was noted for the subset of studies that involved an educational component (N=17; d=0.30, 95% CI: 0.19-0.42, $p<0.001$). Again the heterogeneity disappeared but the effect remained statistically significant after removal of the outlier study (N=16, d=0.23; 95% CI: 0.15-0.31, $p<0.001$). Since three of the educational studies incorporated an additional intervention, the overall analysis was repeated after removing data from those studies. The effect remained significant both before (N=15, d=0.29, 95% CI: 0.16-0.42, $p<0.001$) and after the outlier study was removed (N=14, d=0.21, 95% CI: 0.13-0.30, $p<0.001$).

There was also evidence that interventions incorporating a consumer contact component were effective. The pooled effect was statistically significant and moderate in magnitude (N=5, d=0.47, 95% CI: 0.17-0.78, $p<0.01$), although the level of heterogeneity was significant. The magnitude of the pooled effect size for the three consumer contact studies that did not incorporate an adjunct was similar, but failed to attain statistical significance (d=0.41, 95% CI: −0.15 to 0.98, p=0.15).

There was no evidence that cognitive behavior therapy significantly reduced stigma (d=0.18, 95% CI: −0.47 to 0.84, p=0.58), but the analysis was based on only two studies.

Of the 19 studies, seven involved online delivery and two delivery on a standalone computer. Overall, the pooled effect was statistically significant for both the Internet delivered

Table 1 Summary of randomized controlled trials of stigma interventions included in the meta-analyses

Study	Country	Intervention	Delivery method	Control	Participants (N, group/recruitment)	ITT	Effectiveness	
							Short-term	Follow-up
Personal/public stigma								
Depression								
Corrigan et al (27)	USA	Educ	Group	AC	152, students/local community college	No	No	NA
		Cont	Group				Yes	
		Prot	Group				No	
Griffiths et al (17)	Australia	CBT	Online	AC	525, general population/ electoral roll	Yes	Yes	NA
		Educ	Online				Yes	
Jorm et al (38)	Australia	Educ	Materials	WLC	262, general public/ advertisement-MH services	Yes	Yes	Yes (6 mths)
			Computer				Yes	
Jorm et al (39)	Australia	Educ	Group	WLC	327, teachers/school	Yes	2/7*	1/7* (6 mths)
			Teaching		1,633, students/school		NA	No*
Kiropoulos et al (41)	Australia	Educ	Online	AC	202, first generation Italian & Greek immigrants/ advertising	No	Yes	Yes (1 wk)
Farrer et al (32)	Australia	Educ/CBT	Online	No Int.	155, general population/ MH telephone counselling service	Yes	Yes	No (12 mths)
		Educ/CBT+ Tel counsel	Online+ telephone				No	No
Gulliver et al (37)	Australia	Educ	Online	No Int.	120, elite athletes/direct contact via professional group	Yes	Yes	No (3 mths)
Postnatal depression								
Dias-Vieira (50)	USA	Educ	Materials	AC	507, students/university	No	Yes	NA
Anxiety								
Gulliver et al (37)	Australia	Educ	Online	No Int.	120, elite athletes/direct contact via professional group	Yes	No	Yes (3 mths)
Schizophrenia/psychosis								
Corrigan et al (27)	USA	Educ	Group	AC	152, students/local community college	No	No	NA
		Cont					No	
		Prot					No	
Penn et al (52)	USA	Cont	Video	No Int.	158, students/university	No	0/3*	NA
Corrigan et al (29)	USA	Educ	Group	No Int.	103, students/local community college	No	2/6	NA
Jorm et al (38)	Australia	Educ	Materials	WLC	262, general public/ advertisement-MH services	Yes	Yes	No (6 mths)
			Computer				Yes	Yes
Blair Irvine et al (23)	USA	Educ	Online	No Int.	172, licensed health care staff/advertisement-MH services	Yes	5/9	3/9 (8 wks)
"*Mental illness*"/"*mental health problems*"/*psychological distress*								
Sharp (47)	USA	Educ	Computer	AC	181, students/university	No	0/3	No (4wks)
			Group				0/3	
Finkelstein et al (33)	Russia	Educ	Online	No Int.	193, students/university	No	2/2	2/2 (6 mths)
			Materials				2/2	2/2
Brown et al (24)	USA	Cont	Video	No Int.	143, students/university	No	Yes	Yes (1 wk)
		HalSim	Audio				No	No

Table 1 Summary of randomized controlled trials of stigma interventions included in the meta-analyses *(continued)*

Study	Country	Intervention	Delivery method	Control	Participants (N, group/recruitment)	ITT	Effectiveness	
							Short-term	Follow-up
Campbell et al (25)	UK	Educ + Cont	Group	No Int.	112, school children/school	No	Yes*	No* (10 wks)
Substance abuse								
Corrigan et al (27)	USA	Educ	Group	AC	152, students/local community college	No	Yes	NA
		Cont					No	
		Prot					No	
Social distance								
Depression								
Kitchener & Jorm (42)	Australia	Educ	Group	WLC	301, government employees/direct contact via professional group	Yes	NA	Yes (5 mths)
Jorm et al (38)	Australia	Educ	Materials	WLC	262, general public/ advertisement-MH services	Yes	Yes	No (6 mths)
			Computer				No	No
Schizophrenia/psychosis								
Penn et al (52)	USA	Cont	Video	No Int.	158, students/university	No	No	NA
Kitchener & Jorm (42)	Australia	Educ	Group	WLC	301, government employees/direct contact via professional group	Yes	NA	No (5 mths)
Jorm et al (38)	Australia	Educ	Materials	WLC	262, general public/ advertisement-MH services	Yes	No	No (6 mths)
			Computer				Yes	Yes
Schizophrenia & depression (undifferentiated)								
Jorm et al (51)	Australia	Educ	Group	WLC	753, rural population/ advertising	Yes	NA	Yes (4 mths)
"*Mental illness*"								
Wood & Wahl (48)	USA	Educ + Cont	Group	AC	114, students/university	Yes	Yes	NA
Finkelstein et al (33)	Russia	Educ	Online	No Int.	193, students/university	No	Yes	Yes (6 mths)
			Materials				Yes	Yes
Bayar et al (21)	Turkey	Educ	Online (e-mail)	No Int.	205, mental health professionals (psychiatry residents and specialists)/e-mail network	No	Yes	NA
Brown et al (24)	USA	Cont	Video	No Int.	143, students/university	No	Yes	Yes (1 wk)
		HalSim	Audio				No	No
Perceived stigma								
Depression								
Griffiths et al (17)	Australia	CBT	Online	AC	525, general population/ electoral roll	Yes	Negative	NA
		Educ	Online				No	
Jorm et al (38)	Australia	Educ	Materials	WLC	262, general public/ advertisement-MH services	Yes	No	No (6 mths)
			Computer				No	No
Jorm et al (39)	Australia	Educ	Group	WLC	327, high school teachers/ school	Yes	1/7*	1/7* (6 mths)
			Teaching		1,633, students/school		NA	1/7*
Kiropoulos et al (41)	Australia	Educ	Online	AC	202, first generation Italian & Greek immigrants/ advertising	No	No	No (1 wk)

Table 1 Summary of randomized controlled trials of stigma interventions included in the meta-analyses *(continued)*

Study	Country	Intervention	Delivery method	Control	Participants (N, group/recruitment)	ITT	Effectiveness	
							Short-term	Follow-up
Psychotic disorders								
Fung et al (34,35)	Hong-Kong	Educ + CBT + MI + SST	Group	AC	66, people with schizophrenia/MH service	Yes	No	NA
Jorm et al (38)	Australia	Educ	Materials	WLC	262, general public/ advertisement-MH services	Yes	No	No (6 mths)
			Computer				No	No
"*Mental illness*"								
Aho-Mustonen et al (20)	Finland	Educ	Group	TAU	39, people with schizophrenia in forensic hospital settings/MH service	Yes	No*	NA
Self/internalized stigma								
Psychotic disorders								
Fung et al (34,35)	Hong-Kong	Educ + CBT + MI + SST	Group	AC	66, people with schizophrenia/MH service	Yes	1/3	NA
"*Mental illness*"								
Luoma et al (43)	USA	ACT + M	Group	TAU	133, individuals in a residential addictions treatment program/ substance use service	Yes	No	Yes (4 mths)
Yanos et al (49)	USA	Educ + Cont NE + CR	Group	TAU	39, people with schizophrenia spectrum disorder and high internalized stigma/ mental health and community services	Yes	No*	No* (3 mths)

ITT – intention-to-treat analysis, ACT – acceptance commitment therapy, CBT – cognitive behavior therapy, Cont – contact, Counsel – counseling, CR – cognitive restructuring, Educ – education, HalSim – hallucination simulation, M – mindfulness, MI – motivational interviewing, NE – narrative enhancement, Prot – protest, SST – social skills training, Tel – telephone, AC – attention control, No Int. – no intervention, TAU – treatment as usual, WLC – waitlist control, MH – mental health, NA – not available, NR – not reported, x/y – x out of y scales or subscale items reported were significant

*Effect size factored in baseline scores (in the absence of data suitable for computing a mean standardized difference at post-test)

interventions (N=7, d=0.36, 95% CI: 0.10-0.63, p<0.01) and the non-computerized interventions (N=10, d=0.23, 95% CI: 0.13-0.33, p<0.001). There was no statistically significant difference between the effectiveness of the Internet and non-Internet delivery (Q (1)=0.84, p=0.36). The pattern of findings remained the same after removal of the outlier study (41).

There was little evidence that the conclusions were compromised by publication bias. The classic fail-safe N value for the overall meta-analysis indicated that it would require 218 additional studies reporting null results for the p value to change to exceed 0.05. Similarly, the fail-safe N for educational and standalone educational interventions across all conditions was 216 and 157, respectively. A total of 26 additional studies reporting null results would be required to change the p value to exceed 0.05 for the interventions involving contact and 5 for interventions involving contact alone. The estimated effect sizes were unchanged when Duval and Tweedie trim and fill values were used for all interventions, for standalone educational interventions alone, and for contact interventions alone. The imputed point estimate based on a trim and fill analysis was somewhat reduced for all conditions involving an educational component, but remained statistically significant (d=0.22, 95% CI: 0.08-0.36, p<0.01).

There was also evidence that interventions designed to reduce the stigma associated with depression were effective. The pooled mean effect size for depression across all interventions was significant, albeit small (N=8, d=0.36, 95% CI: 0.10-0.60, p<0.01). The significant level of heterogeneity across studies disappeared when the outlier study (41) was removed, but the pooled mean effect size remained statistically significant (d=0.19, 95% CI: 0.06-0.33, p<0.01). Interventions containing an educational component were associated with a significant reduction in stigma (d=0.36, 95% CI: 0.14-0.59, p<0.01), with the effect remaining statistically significant (d=0.22, 95% CI: 0.09-0.36, p<0.001) but heterogeneity in data disappearing with the exclusion of the

Table 2 Meta-analysis of studies comparing the effects of interventions on personal stigma

	N	d (95% CI)	Z	p	Q	p	I^2	Fail safe N
All conditions								
All interventions	19	**0.28 (0.17-0.39)**	4.88	<0.001	36.55	0.006	50.75	210
excluding outlier	18	**0.22 (0.14-0.29)**	5.52	<0.001	16.85	0.46	0.00	134
Educational interventions	17	**0.30 (0.19-0.42)**	5.14	<0.001	32.12	0.01	50.18	216
excluding outlier	16	**0.23 (0.15-0.31)**	5.80	<0.001	13.53	0.56	0.00	133
Educational interventions with no adjunct	15	**0.29 (0.16-0.42)**	4.40	<0.001	31.83	0.004	56.02	157
excluding outlier	14	**0.21 (0.13-0.30)**	5.08	<0.001	2.2	0.51	0.00	87
Interventions with consumer contact	5	**0.47 (0.17-0.78)**	3.01	0.003	10.38	0.04	61.45	26
with no adjunct	3	0.41 (−0.15 to 0.98)	1.44	0.15	9.34	0.009	78.58	-
CBT interventions	2	0.18 (−0.47 to 0.84)	0.55	0.58	4.65	0.03	78.48	-
with no adjunct	1	-	-	-	-	-	-	-
Depression								
All interventions	8	**0.36 (0.10-0.60)**	2.81	0.005	23.76	0.001	70.54	47
excluding outlier	7	**0.19 (0.06-0.33)**	2.81	0.005	5.31	0.50	0.00	
Educational interventions	8	**0.36 (0.14-0.59)**	3.15	0.002	19.91	0.006	64.84	52
excluding outlier	7	**0.22 (0.09-0.36)**	3.25	0.001	3.04	0.80	0.00	15
Educational interventions with no adjunct	7	**0.34 (0.10-0.59)**	2.74	0.006	19.25	0.004	68.83	38
Interventions with consumer contact	0	-	-	-	-	-	-	-
CBT interventions	2	0.18 (−0.47 to 0.84)	0.55	0.58	4.65	0.03	78.48	-
with no adjunct	1	-	-	-	-	-	-	
Mental illness/distress								
All interventions	6	**0.30 (0.10-0.50)**	2.95	0.003	8.80	0.12	43.15	19
Educational interventions	5	**0.34 (0.12-0.56)**	2.98	0.003	7.62	0.11	47.54	18
with no adjunct	3	**0.22 (−0.04 to 0.47)**	1.67	0.094	3.30	0.19	39.19	1
Interventions with consumer contact	3	**0.68 (0.40-0.95)**	4.84	<0.001	2.64	0.27	24.32	22
with no adjunct	1	-	-	-	-	-	-	-
Schizophrenia/psychosis								
All interventions	6	**0.20 (0.06-0.34)**	2.81	0.005	3.22	0.67	0.00	7
Educational interventions	5	**0.23 (0.08-0.37)**	2.97	0.003	1.03	0.91	0.00	7
with no adjunct	2	0.15 (−0.14 to 0.45)	1.01	0.31	0.16	0.69	0.00	-
Interventions with consumer contact	2	0.14 (−0.18 to 0.45)	0.84	0.40	0.70	0.40	0.00	-

Statistically significant data are highlighted in bold. The outlier is the study by Kiropoulos et al (41)
CBT – cognitive behavior therapy

outlier (41). The pattern of findings was not altered when those educational interventions with an adjunct component were excluded from the analysis (d=0.34, 95% CI: 0.10-0.59, p<0.01). No study focused on the effect of contact on depression. There was no evidence that cognitive behavior therapy significantly reduced stigma (N=2; d=0.18, 95% CI: −0.47-0.84, p=0.58).

There was little evidence that the conclusions for depression stigma were compromised by publication bias. The fail-safe N for the studies reporting depression stigma was 47 for all interventions, and 52 and 38 for studies involving an educational component or an educational intervention alone. The estimated effect sizes for all the depression studies were unchanged when Duval and Tweedie trim and fill values were used, as were those for educational interventions without an adjunct. For the subset of studies with an educational component, the trim and fill imputed effect size estimate was 0.16 (95% CI: 0.04-0.29) compared to 0.22.

Interventions in studies employing a generic mental illness or mental health stigma measure were also effective both when all intervention types were incorporated (d=0.30, 95% CI: 0.10-0.50, p<0.01) and for the subset involving educational interventions (d=0.34, 95% CI: 0.12-0.56, p<0.01), although educational interventions without an

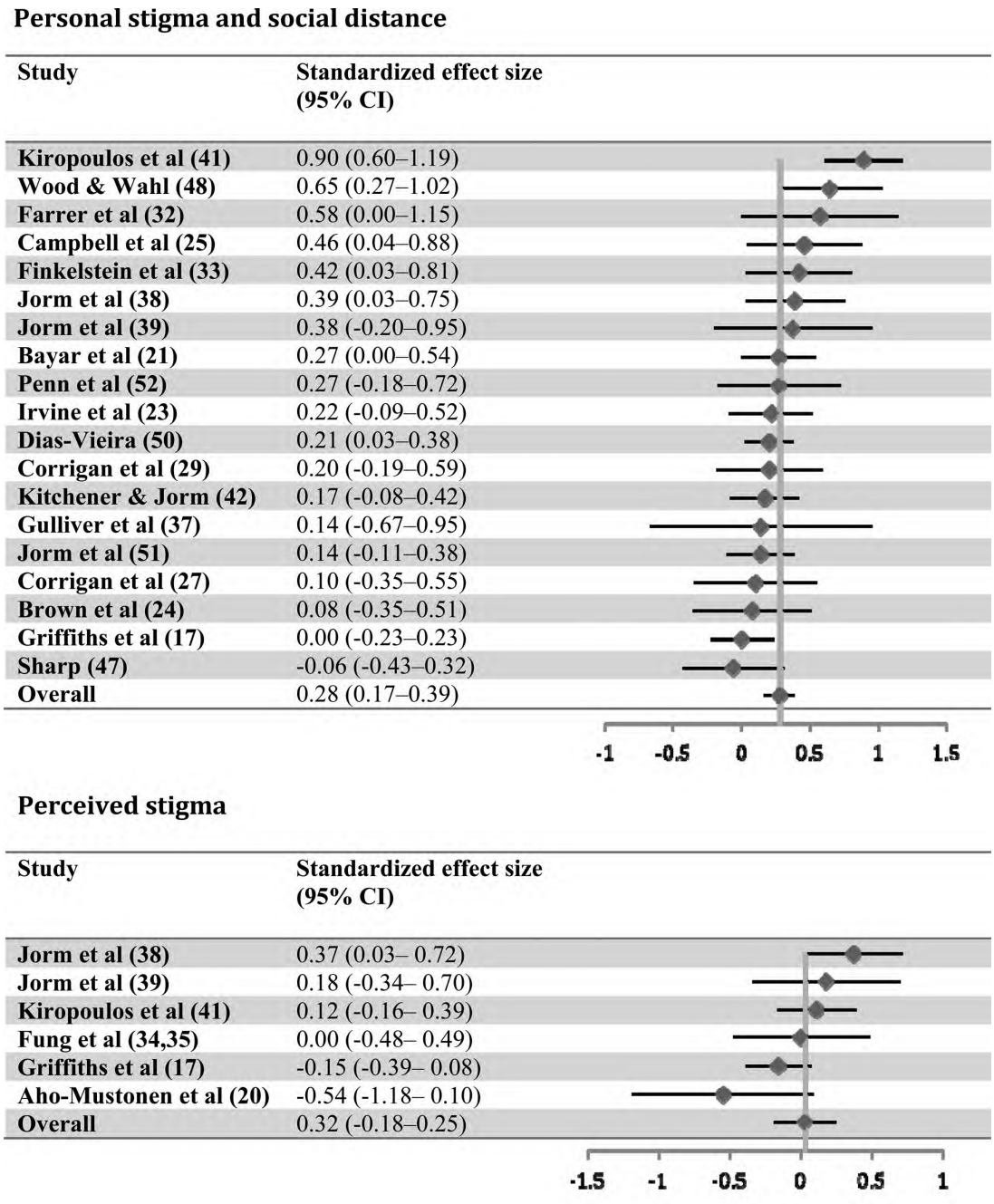

Figure 2 Forest plot showing the effect of stigma interventions (random effects model; a positive effect signifies a decrease in stigma)

adjunct (d=0.22, 95% CI: −0.04 to 0.47) just failed to attain statistical significance (p=0.09). There was also evidence that interventions incorporating consumer contact were effective, the pooled effect size being moderate (d=0.68, 95% CI: 0.40-0.95) and statistically significant (p<0.001).

In general, the risk of publication bias for these studies was not high. The fail-safe N was 19 for all interventions, and 18 and 21 for those involving an educational component and contact, respectively. The estimated effect sizes for the combined interventions were unchanged when the Duval and Tweedie trim and fill values were used. The effect size for all education intervention studies was 0.22 (95% CI: −0.01 to 0.44, p=0.05) compared to 0.34. For educational interventions alone, the trim and fill value was unchanged.

Overall, the interventions which targeted psychosis or schizophrenia were effective. The pooled mean effect size was significant for all interventions combined (N=6, d=0.20, 95% CI: 0.06-0.34, p<0.01) and for the subset of interventions incorporating an educational component (d=0.23, 95% CI: 0.08-0.37, p<0.01). The meta-analysis of the two educational interventions with no adjuncts (d=0.15, 95% CI: −0.14 to 0.45) failed to attain statistical significance (p=0.31).

Similarly, the meta-analysis of the two interventions involving consumer contact (neither included adjuncts) did not yield a statistically significant effect (N=2, d=0.14, 95% CI: −0.18 to 0.45, p=0.40). Heterogeneity was not statistically significant for any of the analyses involving psychosis/schizophrenia. The fail-safe N for the studies was 7 for all interventions, and 7 for studies involving an educational component. The imputed point estimate based on Duval and Tweedie trim and fill analysis was somewhat reduced for the combined interventions targeting psychosis/schizophrenia, but remained statistically significant (d=0.16, 95% CI: 0.02-0.29, p<0.05). The estimated effect size for interventions with an educational component was unchanged. Publication bias measures could not be imputed for the contact or the education without adjunct interventions, as more than two studies are required to undertake these analyses.

Perceived stigma

Six of the eight trials evaluating the effect of interventions on perceived stigma generated data from which it was possible to compare the effect of an intervention vs. a control condition (17,20,34,35,38,39,41). The data reported in the omitted two trials (44,46) were not in a form from which we could confidently calculate a suitable effect size. The outcome of the meta-analysis of the perceived stigma studies is summarized in Table 3.

Overall, the interventions did not significantly reduce perceived stigma. The forest plot is depicted in Figure 2. The pooled mean effect size across all conditions (d=0.03, 95% CI: −0.19 to 0.25) was not significant (p=0.77). Similar null effects were obtained for the interventions involving an educational component and for those containing only an educational component. The heterogeneity was moderate, but not statistically significant. A null effect was also found for cognitive behavior therapy; heterogeneity was low. There were no other interventions with more than one study.

A similar pattern of findings was evident in the studies that specifically targeted depression. The pooled mean effect size across all interventions was not statistically significant (d=0.11, 95% CI: −0.15 to 0.37, p=0.39). Nor was the pooled mean effect size for educational interventions (all of which were standalone) statistically significant. The heterogeneity was moderate, but did not attain statistical significance. There were no other interventions with more than one study.

There were no studies of the effect of interventions for generic mental illness. The pooled mean effect size across the two studies targeting perceived psychosis or schizophrenia stigma was not statistically significant (d=0.21, 95% CI: −0.10 to 0.52, p=0.18). Both involved an educational component. Heterogeneity was low and non-significant.

Internalized stigma

The outcome of the meta-analysis of the internalized stigma studies is summarized in Table 3. All three of the trials evaluating the effect of interventions on self-stigma generated data from which it was possible to compare the effect of an intervention vs. a control condition (34,35,43,49). Two of the trials employed measures which focused on general mental illness and a third focused on schizophrenia. Each of the studies incorporated a form of psychotherapy intervention (cognitive behavior therapy, cognitive restructuring, or acceptance and commitment therapy). The pooled mean effect size across the three studies was not statistically significant (0.16; 95% CI: −0.41 to 0.73, p=0.57). There was substantial, significant heterogeneity in effect sizes.

DISCUSSION

Overall, the assessed interventions were associated with a small, but significant reduction in personal stigma. The effect was significant when outcomes from all studies were combined regardless of type of mental disorder and intervention. It was also significant when analyses were restricted to the stigma associated with depression, “mental illness”, and psychosis/schizophrenia.

Educational interventions alone or when combined with other interventions were consistently associated with a reduction in personal stigma for different types of mental disorder. The exception was that standalone educational interventions failed to attain statistical significance for schizophrenia/psychosis.

There were few randomized controlled trials of the effect of consumer contact. There was evidence of the effectiveness of interventions incorporating contact when outcomes from all studies targeting personal stigma were combined regardless of mental disorder, but the effect did not retain statistical significance when the analysis was restricted to studies involving consumer contact without an adjunct. Nor was there evidence that contact was associated with a reduction in stigma for schizophrenia/psychosis. Interventions with a consumer contact element were associated with a reduction in stigma associated with “mental illness”, but there were insufficient studies investigating the effect of consumer contact alone on “mental illness” stigma.

Cognitive behavior therapy was not effective in reducing personal stigma, but the evidence is limited to date.

There were fewer studies of the effectiveness of interventions for reducing perceived and internalized stigma. Overall, however, the meta-analyses did not find evidence of the effectiveness of interventions for reducing these two types of stigma.

The present meta-analysis confirms Corrigan et al’s (14) finding that current stigma interventions are effective in reducing personal stigma. This replication is important given that, in contrast to Corrigan et al’s study, we pooled independent effect sizes. In addition, for the first time, the current analysis provides quantitative evidence that stigma interventions are effective for specific categories of mental disorder, including depression and psychosis/schizophrenia.

Table 3 Meta-analyses of studies comparing the effects of interventions on perceived stigma and internalized stigma

	N	d (95% CI)	Z	p	Q	p	I^2	Fail safe N
Perceived stigma								
All conditions								
All interventions	6	0.03 (−0.19 to 0.25)	0.29	0.77	9.92	0.078	49.60	0
Educational interventions	6	0.04 (−0.17 to 0.25)	0.37	0.71	9.27	0.10	46.04	0
with no adjunct	5	0.04 (−0.20 to 0.29)	0.34	0.34	9.25	0.06	56.77	0
CBT interventions	2	−0.15 (−0.36 to 0.07)	−1.36	0.17	0.47	0.49	0.00	-
Depression								
All interventions	4	0.11 (−0.15 to 0.37)	0.86	0.39	7.05	0.06	60.26	0
Educational interventions	4	0.12 (−0.12 to 0.36)	0.96	0.34	6.75	0.08	55.58	0
Mental illness								
All interventions	1	-	-	-	-	-	-	-
Schizophrenia/psychosis								
All interventions	2	0.21 (−0.10 to 0.52)	1.35	0.18	1.18	0.28	15.35	-
Internalized stigma								
All conditions								
All interventions	3	0.16 (−0.41 to 0.73)	0.57	0.57	7.69	0.02	74.00	0

CBT – cognitive behavior therapy

However, it is clear that intervention research for personal stigma has neglected other types of mental disorder, with only one published study targeting generalized anxiety disorder (37), two focused on substance abuse (22,27) and no studies targeting a range of other conditions such as bipolar disorder, panic disorder, social anxiety, post-traumatic stress disorder and eating disorders. There is clearly a need to undertake further research to evaluate the effectiveness of stigma reduction interventions for these conditions.

The current study confirms that both interventions with an educational component and those with a consumer contact component are effective in reducing stigma. However, standalone educational interventions for schizophrenia and psychosis did not achieve statistical significance. Further investigation of the effectiveness of standalone educational interventions for these conditions is required. Moreover, although interventions with a consumer contact component were effective overall, there was insufficient evidence from the meta-analysis to conclude that contact alone was effective, or that contact was effective in reducing stigma associated to depression or schizophrenia/psychosis. Again, there is a clear need for further research investigating the effect of consumer contact, whether there is a difference in the effectiveness of contact, education and education combined with contact, and whether any effects of contact differ across different mental disorders.

A striking finding of the research was the small effect sizes obtained. Further research is needed to develop more effective interventions and to investigate the value of targeting specific at-risk groups. In their Australian national study of predictors of personal stigma, Griffiths et al (4) reported that older people and people who were born outside Australia had a higher level of personal stigma than their counterparts. Kiropoulos et al (41) targeted older, non-English speaking residents in their Australian intervention study. This might explain in part why the latter trial yielded the highest effect size of any of the studies targeting personal stigma, although the lack of follow-up may be another explanation. Consideration might be given to specifically targeting those at highest risk of personal stigma, who for depression and generalized anxiety disorder include for example men and those with less contact with people with a mental illness (4,58).

Although we found evidence that available interventions can reduce personal stigma, our findings suggest that interventions to date have failed to reduce perceived stigma. None of the comparisons undertaken yielded statistically significant effects. Further, compared with personal stigma, few studies have focused on interventions to reduce perceived stigma. This is not surprising if we assume that perceived stigma is an accurate representation of the actual levels of stigma in the community. However, employing parallel measures of personal and perceived stigma, Griffiths et al (4,6) reported data suggesting that the public may overestimate the extent of stigma in the community, a finding that has subsequently been reported by others employing the same scales (59,60). Since perceived stigma may be a barrier to help-seeking among consumers with a mental illness (61)

and may prevent those with a mental illness from seeking appropriate adjustments in the workplace, there is a need to devise interventions that are effective in reducing that kind of stigma.

The paucity of studies (N=3) investigating interventions for internalized stigma and the absence of effective interventions for reducing this type of stigma is a matter of significant concern. Of the interventions investigated, each employed a cognitive or cognitive behavioral therapy (including acceptance and commitment therapy). There is a need to determine if such interventions can be better tailored to reduce stigma and also to consider alternative approaches that might be effective. If self-stigma represents an internalization of negative community attitudes (62), it is possible that interventions that are effective in reducing perceived stigma might also reduce self-stigma.

The finding that stigma interventions delivered via the Internet were at least as effective as interventions delivered using other means raises the possibility that Internet delivery may be an effective vehicle for stigma reduction programs en-masse. Currently many school-based and workplace stigma reduction programs are delivered face-to-face. This has substantial resource implications, and the quality of the training may vary between trainers. Online interventions can be delivered more flexibly, with fewer personnel and resources and with high fidelity. Cost considerations are particularly important in the context of small effect sizes.

It is clear that most high-quality stigma-intervention research has been undertaken among students in tertiary settings and that in particular there is a paucity of studies among members of the general community, health professionals, the workplace, in schools, among teachers and university lecturers, among culturally and linguistically diverse groups and in the defence force. Further, very little stigma intervention research has been undertaken outside the United States and Australia or in low and middle income countries, and only 20% of the studies have undertaken follow-ups of 6 months or more. Finally, there is a need to improve the quality of studies in the area, particularly with respect to reducing attrition bias and employing appropriate intention-to-treat analyses as well as reducing performance bias.

The main limitation of our meta-analyses is the paucity of studies that had investigated the effects of stigma interventions for different types of mental disorder and for different intervention types, particularly in the case of consumer contact. This limited the conclusions that could be drawn about the relative effects of interventions as a function of mental disorder or intervention type. In addition, we largely restricted our analyses to studies that published the data required for calculating effect sizes. Finally, our review was confined to published studies in the English language.

In conclusion, our meta-analyses suggest that current stigma interventions are effective in reducing personal stigma. Further research is required to establish whether stigma interventions can be effective for perceived or internalized stigma and for particular types of mental disorders. There is also a need to further investigate the effectiveness of consumer contact in reducing stigma and its effectiveness relative to educational interventions. Overall, the effect sizes were small and further research is clearly required to develop new more effective interventions for reducing stigma. The Internet may prove a cost-effective means of delivering current interventions. Finally, there is a paucity of research investigating the effectiveness of stigma interventions in schools and in the workplace, although they represent an obvious setting for disseminating stigma reduction programs worldwide.

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Predictors of type 2 diabetes in a nationally representative sample of adults with psychosis

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Antipsychotic drugs such as clozapine and olanzapine are associated with an increased risk for type 2 diabetes, but relatively little is known about the relationship between risk factors for type 2 diabetes established in the general population and type 2 diabetes in people with psychosis. We estimated the prevalence of established risk factors and their association with type 2 diabetes in a nationally representative sample of people with an ICD-10 psychosis (N=1642) who gave a fasting blood sample (N=1155). Logistic regression was used to summarize associations adjusted for age and sex. In this sample, whose mean duration of psychosis was 14.7 years, 12.1% (13.1% of women and 11.5% of men) had type 2 diabetes at age 18–64 years based on current fasting blood glucose levels or treatment with a hypoglycaemic drug. Risk was greatly increased in young adults compared with the general population and peaked in middle age. Risk factors in the general population were common in people with psychosis and strongly associated with type 2 diabetes in those people. Treatment with clozapine was associated with an increased risk and treatment with olanzapine with a decreased risk for type 2 diabetes. The development of diabetes or pre-diabetes may therefore influence the likelihood of treatment with olanzapine over time. The strongest predictors of type 2 diabetes in a multivariate model were a body mass index of at least 40 and treated hypercholesterolemia, followed by a body mass index between 35 and 39.9, a family history of diabetes and treated hypertension. There was minimal to no confounding of the association between type 2 diabetes and current clozapine or olanzapine treatment, but neither association remained significant after adjustment for other predictors. Longitudinal relationships among predictors are likely to be complex, and previous antipsychotic drug treatment may at least partly explain risks associated with severe obesity, dyslipidemia and hypertension. A focus on weight loss is warranted in people with psychosis, but prevention strategies for type 2 diabetes should be broadened to include those with emerging dyslipidemia, hypertension and a family history of diabetes.

Key words: Type 2 diabetes, psychosis, risk factors, clozapine, olanzapine, body mass index, hypercholesterolemia, hypertension

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The co-occurrence of diabetes and schizophrenia has been noted for over a century (1,2). A recent analysis of this comorbidity using prospectively collected Danish population registry data provided strong evidence that there is an increased risk for type 2 diabetes in people with schizophrenia both before (3) and especially after exposure to antipsychotic drugs (4).

Among those taking the commonly prescribed second generation antipsychotic drugs, the risk of developing type 2 diabetes during the first 6 years is greatest for clozapine and olanzapine. The former is used in many parts of the world for treatment-resistant cases of schizophrenia (5), while the latter is one of the most commonly prescribed antipsychotic drugs (6).

The increased risk for type 2 diabetes in association with antipsychotic drug treatment and interventions directed at related weight gain have deservedly received substantial attention (7-13). Much less attention has been paid to other risk factors which contribute to the context within which treatment effects are expressed.

Type 2 diabetes in the general population is a complex multifactorial disease (14). Established risk factors include increasing age, obesity, sedentary lifestyle, diet, family history, hypertension, elevated cholesterol and gestational diabetes (15). The interpretation of the observed association between antipsychotic drug treatment and risk for type 2 diabetes has been queried in the past because established risk factors have not been controlled for and may therefore be an important source of unmeasured confounding (16,17). The above-mentioned Danish study (4), for example, could control for only age, sex, blood pressure medication and cholesterol medication.

The importance of risk factors for type 2 diabetes established in the general population has not yet been explored in a large representative cohort of adults with psychosis, and we therefore do not know which factors should be tested as potential confounders of the observed association between type 2 diabetes and antipsychotic drug treatment. The aims of this study were: a) to estimate the prevalence, in a national sample of adults with psychosis, of the risk factors for type 2 diabetes established in the general population; b) to estimate the association of those factors with type 2 diabetes in the above-mentioned sample and c) to test if they confound the observed cross-sectional association between type 2 diabetes and treatment with clozapine or olanzapine.

Table 1 The prevalence of current type 2 diabetes by age and gender in a national sample of adults with psychosis

Age	Total (N=1155) % (95% CI)	Women (N=444) % (95% CI)	Men (N=711) % (95% CI)
18-24	5.8 (2.8-11.5)	5.3 (1.5-17.3)	6.0 (2.6-13.3)
25-34	7.1 (4.9-10.2)	9.0 (5.1-15.4)	6.1 (3.7-9.8)
35-44	11.7 (8.6-15.7)	13.3 (8.6-20.1)	10.4 (6.8-15.7)
45-54	21.3 (16.6-26.9)	19.2 (12.6-28.0)	22.8 (16.7-30.2)
55-64	17.1 (11.1-25.5)	16.0 (8.3-28.5)	18.2 (10.2-30.3)
18-64	**12.1 (10.4-14.1)**	**13.1 (10.2-16.5)**	**11.5 (9.4-14.1)**

METHODS

The Australian National Survey of Psychosis is a population-based cross-sectional study with a target population defined by psychosis, place of residence, age 18-64 years and contact with public mental health services or relevant non-government organizations (18). The study was conducted in 2010 at seven sites across the five mainland Australian states. The research protocol for the study was approved by relevant institutional ethics committees and all participants gave written informed consent.

Data analysed here are for participants with a diagnosis of non-organic psychosis (N=1642) who also gave a fasting blood sample (N=1155). This subset of the cohort comprised individuals with schizophrenia (51.2%, 591/1155); bipolar disorder with psychotic features (19.5%, 225/1155); schizoaffective disorder (18.2%, 210/1155); depressive psychosis (5.5%, 63/1155) and delusional disorders or other non-organic psychoses (5.7%, 66/1155).

The Diagnostic Interview for Psychosis (19) was used to diagnose psychosis following the ICD-10. Mean duration of illness was estimated by self-report. Current type 2 diabetes was diagnosed, according to the American Diabetes Association (20), on the basis of a current fasting blood glucose of at least 7.0 mmol/L or a current drug treatment for hyperglycaemia. Our diagnosis of type 2 diabetes did not include an oral glucose tolerance test, which is difficult to obtain in people with psychosis.

Central obesity was defined as a waist circumference of at least 94 cm in men or 80 cm in women. Obesity was subdivided into class I (a body mass index of at least 30 but lower than 35), class II (a body mass index of at least 35 but lower than 40) and class III (a body mass index of at least 40). Dietary adequacy was estimated by the number of servings of fruit and vegetables consumed daily in the past week (those consuming at least two serves of fruit and five serves of vegetables were coded as having an adequate intake). The level and frequency of physical activity during the previous week was assessed using the International Physical Activity Questionnaire (21), and defined as a four-category variable (1 – any level of vigorous activity, at least once for at least 10 consecutive minutes; 2 – any level of moderate activity, at least once for at least 10 consecutive minutes; 3 – any walking, at least once for at least 10 consecutive minutes; 4 – no activity, i.e., not 1 or 2 or 3). Family history of diabetes in first-degree relatives was assessed by self-report.

Current prescribed medication use during the past four weeks was recorded based on participant report, with inspection of pill bottles or medication chart review for those in hospital at the time of interview. Current antipsychotic drug treatment was coded as a four category variable (1 – clozapine but not olanzapine; 2 – olanzapine but not clozapine; 3 – clozapine and olanzapine; 4 – anything else, i.e., any other antipsychotic drug treatment or no antipsychotic drug treatment).

The 95% confidence interval for the estimated prevalence of type 2 diabetes was calculated using STATA version 12.1 (22). All other data analysis was conducted using SPSS Version 21 (23). Logistic regression was used to estimate associations with type 2 diabetes. Univariate and multivariate odds ratios were adjusted for age (because risk for type 2 diabetes increases with age in the general population, and our cohort varied in age between 18 and 64 years) and for gender (because men are at slightly greater risk than women in the general population, and in our cohort there was an unequal sex ratio). Sex differences in the prevalence of risk factors were assessed using a two-tailed Pearson chi-square test. Sex differences in the association of risk factors with type 2 diabetes were assessed by the Wald test. Bias associated with giving a fasting blood sample was assessed by comparing those who gave a sample with those who declined using a two-tailed Pearson chi-square test.

RESULTS

Among the subsample of participants with an ICD-10 diagnosis of psychosis who gave a fasting blood sample (N=1155/1642), 61.6% (711/1155) were male and 38.4% (444/1155) were female. Their mean age was 38.4±11.0 years (range=18–64 years) and their mean duration of psychotic illness was 14.7±10.2 years (range=0-50 years).

One hundred and forty patients (12.1%) met the American Diabetes Association's criteria for type 2 diabetes based on current fasting blood glucose levels or current hypoglycaemic drug treatment (Table 1). The prevalence of type 2 diabetes was non-significantly higher in women (13.1%, 58/444) than in men (11.5%, 82/711) ($\chi^2=0.67$, $p=0.45$). The prevalence was 5.8% and 7.1%, respectively, among people aged 18–24 and 25–34 years, while it was 0.3% in people aged 25–34 years in the latest Australian general population survey (24). The prevalence increased with age, with a peak (21.3%) among people aged 45–54 years (Table 1).

In the univariate analysis, after adjustment for age and gender, the risk for type 2 diabetes was significantly increased in association with class I-III obesity, central obesity, treated hypercholesterolemia, treated hypertension, family history of diabetes and current treatment with clozapine (Table 2). The risk was significantly decreased in association with at least

Table 2 Univariate associations between risk factors for type 2 diabetes established in the general population and current type 2 diabetes in adults with psychosis

		Total sample (N=1155)				Women (N=444)				Men (N=711)			
Risk factor	**Assessed by**	**%**	**OR**	**95% CI**	**p**	**%**	**OR**	**95% CI**	**p**	**%**	**OR**	**95% CI**	**p**
Obesity	Overweight	30.2	1.38	0.61-3.09	0.43	24.1	3.36	0.70-16.14	0.12	34.0	0.90	0.34-2.39	0.84
	Obese, class I	23.4	2.76	1.27-5.99	0.01	22.5	3.15	0.64-15.39	0.15	24.0	2.66	1.08-6.52	0.03
	Obese, class II	13.0	7.28	3.34-15.86	0.0001	16.0	10.40	2.29-47.72	0.003	11.1	6.30	2.48-16.03	0.0001
	Obese, class III	11.7	10.15	4.64-22.18	0.0001	17.6	13.77	3.06-61.84	0.001	8.1	9.34	3.56-24.44	0.0001
	Reference: normal weight	*20.3*				*18.5*				*21.3*			
	Waist ≥84 (female), ≥90 (male)	83.8	2.86	1.35-6.04	0.006	93.7	*	*	*	77.7	2.32	1.08-4.98	0.03
	Reference: normal waist circumference	*16.2*				*6.3*				*22.3*			
Sedentary lifestyle	Any vigorous activity past week (10+ min)	21.7	0.39	0.18-0.83	0.015	17.8	0.49	0.16-1.47	0.20	24.2	0.34	0.12-0.95	0.04
	Any moderate activity past week (10+ min)	20.6	0.70	0.37-1.32	0.27	20.5	0.59	0.22-1.58	0.59	20.7	0.77	0.33-1.79	0.55
	Any walking past week (10+ min)	46.2	1.03	0.61-1.76	0.89	48.6	0.93	0.42-2.04	0.93	44.7	1.12	0.54-2.31	0.75
	Reference: none of the above	11.4				13.1				10.4			
Diet	2+ serves of fruit and 5+ serves of vegetables daily	6.2	1.29	0.65-2.57	0.45	9.0	1.19	0.47-3.01	0.70	4.4	1.43	0.51-3.95	0.48
	Reference: less than the above	*93.8*				*91.0*				*95.6*			
Family history	Self report in first degree relatives	37.3	2.76	1.88-4.03	0.0001	48.1	4.67	2.36-9.23	0.0001	30.5	2.04	1.26-3.30	0.004
	Reference: no reported history	*62.7*				*51.9*				*69.5*			
High blood pressure	Treated with an antihypertensive drug	11.0	3.23	2.04-5.11	0.0001	11.7	3.40	1.65-7.00	0.001	10.5	3.18	1.75-5.76	0.0001
	Reference: no current antihypertensive treatment	*89.0*				*88.3*				*89.5*			
High cholesterol	Treated with a lipid regulating drug	12.6	5.88	3.87-8.92	0.0001	13.3	7.85	4.06-15.15	0.0001	12.1	4.86	2.81-8.40	0.0001
	Reference: no current lipid regulating treatment	*87.4*				*86.7*				*87.9*			
Antipsychotic drugs	Clozapine, not olanzapine	17.7	1.56	1.00-2.43	0.048	13.3	1.71	0.83-3.52	0.14	20.4	1.51	0.86-2.65	0.14
	Olanzapine, not clozapine	18.1	0.51	0.28-0.91	0.02	15.3	0.55	0.21-1.47	0.55	20.8	0.48	0.23-0.99	0.049
	Clozapine + olanzapine	0.6	3.09	0.58-16.45	0.18	0.9	**	**	**	0.4	12.70	1.10-146.13	0.041
	Reference: neither clozapine nor olanzapine	63.6				71.4				58.8			
Male gender	*Reference: female*	61.6	0.97	0.67-1.42	0.90	-	-	-	-	-	-	-	-

Odds ratio for male gender in the total sample is adjusted for age, all other odds ratios in the total sample are adjusted for age and sex; odds ratios in females and males are adjusted for age

*Odds ratio could not be estimated because 100% of women with psychosis and type 2 diabetes had an at-risk waist circumference; **odds ratio could not be estimated because no woman with type 2 diabetes was taking clozapine and olanzapine

10 minutes per week of vigorous physical activity and with current treatment with olanzapine (Table 2).

In the multivariate analysis, after adjustment for age and gender, and all other predictors, the risk for type 2 diabetes was significantly increased in association with class II-III obesity, treated hypercholesterolemia, treated hypertension and family history of diabetes (Table 3). After adjustment for the additive effects of other predictors, the association with treated hypertension and obesity was attenuated by 40–50% and the association with family history of diabetes and treated hypercholesterolemia was attenuated by 20–30%. The estimated associations with use of clozapine and olanzapine were reduced marginally in the total sample, but a little more in men treated with olanzapine or olanzapine plus

Table 3 Multivariate associations between risk factors for type 2 diabetes established in the general population and current type 2 diabetes in adults with psychosis adjusted for age and sex

		Total sample (N=1155)			Women (N=444)			Men (N=711)		
Risk factor	**Assessed by**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Obesity	Overweight	1.12	0.43-2.90	0.80	2.51	0.48-13.10	0.27	0.75	0.22-2.53	0.64
	Obese, class I	1.75	0.65-4.66	0.26	1.62	0.29-8.86	0.57	1.80	0.50-6.47	0.36
	Obese, class II	3.74	1.39-10.10	0.009	4.96	0.97-25.34	0.054	3.40	0.91-12.72	0.069
	Obese, class III	5.49	2.06-14.62	0.001	5.23	1.06–25.78	0.042	6.55	1.74-24.65	0.005
	Reference: normal weight									
	Waist ≥84 (female), ≥90 (male)	0.97	0.34-2.71	0.95	*	*	*	0.82	0.25-2.75	0.76
	Reference: normal waist circumference									
Sedentary lifestyle	Any vigorous activity past week (10+ min)	0.51	0.21-1.23	0.13	0.38	0.08-1.67	0.20	0.67	0.22-2.04	0.48
	Any moderate activity past week (10+ min)	0.83	0.39-1.74	0.62	0.67	0.20-2.27	0.52	0.96	0.36-2.53	0.94
	Any walking past week (10+ min)	1.08	0.58-2.02	0.79	0.90	0.33-2.42	0.83	1.24	0.54-2.84	0.61
	Reference: none of the above									
Diet	2+ serves of fruit and 5+ serves of vegetables daily	0.93	0.40-2.15	0.86	0.65	0.19-2.14	0.48			
	Reference: less than the above									
Family history	Self report in first degree relatives	2.22	1.44-3.44	<0.0001	2.56	1.17-5.59	0.018	1.99	1.14-3.46	0.015
	Reference: no reported history									
High blood pressure	Treated with an antihypertensive drug	1.87	1.08-3.26	0.025	2.23	0.91-5.48	0.08	1.68	0.81-3.47	0.16
	Reference: no current antihypertensive treatment									
High cholesterol	Treated with a lipid regulating drug	4.26	2.64-6.85	<0.0001	6.10	2.79-13.31	<0.0001	3.89	2.03–7.44	<0.0001
	Reference: no current lipid regulating treatment									
Antipsychotic drugs	Clozapine, not olanzapine	1.52	0.91-2.54	0.10	1.50	0.63-3.56	0.33	1.64	0.84-3.17	0.14
	Olanzapine, not clozapine	0.55	0.28-1.08	0.08	0.28	0.07-1.04	0.062	0.72	0.32-1.60	0.42
	Clozapine + olanzapine	2.73	0.39-18.78	0.30	**	**	**	7.46	0.55–99.86	0.13
	Reference: neither clozapine nor olanzapine									
Male gender	*Reference: female*	1.66	1.05-2.64	0.03	-	-	-	-	-	-

In the total sample male gender was significantly associated with risk for type 2 diabetes after adjustment for all other risk factors (OR=1.66, 95% CI: 1.04-2.64, p=0.03), as was age (OR=1.028, 95% CI: 1.006-1.051, p=0.013)
*Odds ratio could not estimated because 100% of women with psychosis and type 2 diabetes had an at-risk waist circumference waist circumference; **odds ratio could not be estimated because no woman with type 2 diabetes was taking clozapine and olanzapine

clozapine. Current treatment with clozapine and olanzapine was not significantly associated with type 2 diabetes in the multivariate model, neither was central obesity nor physical activity. The strongest predictors of current type 2 diabetes in the multivariate model were a body mass index of at least 40 (adjusted OR=5.5) and treated hypercholesterolemia (adjusted OR=4.3). This was true for the total sample as well as for men and women considered separately.

Severe obesity, low levels of physical activity and a positive family history of diabetes were all more common in women than men (Table 4). Current treatment with clozapine or olanzapine was more common in men than women (Table 4). The prevalence of treated hypercholesterolemia and treated hypertension did not vary by gender. Male gender was not significantly associated with risk for type 2 diabetes (Table 2) until after adjustment for all other predictors

Table 4 Sex differences in the prevalence of risk factors for type 2 diabetes established in the general population and their association with current type 2 diabetes in adults with psychosis

		Test for sex difference in prevalence of risk factor	Test for sex difference in association with type 2 diabetes (adjusted for age)
Risk factor	**Assessed by**	**Pearson chi-square**	**Wald test**
General obesity	Obese class I, II, III, over, normal and underweight	42.06 (df=5), p<0.0001, F>M	3.88 (df=5), p=0.56
Central obesity	Waist circumference at-risk vs. not at-risk	63.91 (df=1), p<0.0001, F>M	0.00 (df=1), p=0.99
Sedentary lifestyle	Any vigorous act, moderate act, walking, none of these	8.19 (df=3), p=0.042, F>M	1.09 (df=3), p=0.77
Diet	2+ fruit and 5+ vegetable servings daily	10.08 (df=1), p=0.002, M>F	1.20 (df=1), p=0.78
Family history	Self report in first degree relatives, yes or no	33.03 (df=1), p<0.0001, F>M	4.01 (df=1), p=0.045, F>M
Hypertension	Currently treated with an antihypertensive drug or not	0.92 (df=1), p=0.34	0.09 (df=1), p=0.76
High cholesterol	Currently treated with a lipid regulating drug or not	0.58 (df=1), p=0.46	0.60 (df=1), p=0.43
Antipsychotic drugs	Currently treated with clozapine or not	23.06 (df=1), p<0.0001, M>F	0.01 (df=1), p=0.89
	Currently treated with olanzapine or not	7.89 (df=1), p=0.005, M>F	0.04 (df=1), p=0.83

(Table 3). The association between type 2 diabetes and a family history of diabetes was significantly stronger in women than men (Table 2), but this difference was attenuated after adjustment for other predictors (Table 3).

The prevalence of the risk factors for type 2 diabetes did not differ between those who gave a fasting blood sample and those who did not.

DISCUSSION

Young adults with psychosis in the current survey had a greatly elevated prevalence of type 2 diabetes relative to the general population (24). Current guidelines and recommendations for general practitioners note that people at high risk for undiagnosed type 2 diabetes should be screened, including those taking antipsychotic drugs (25), but do not emphasize that screening in those with psychosis should begin at the earliest possible age. The recently promulgated Healthy Active Lives statement, an international consensus statement on improving the physical health of young people with psychosis, advocates assessment of diabetes risk within one month of antipsychotic drug treatment (26). Assessment prior to antipsychotic drug treatment is desirable to capture baseline risk status, but difficult to obtain when clients are first seeking treatment for acute psychosis.

The peak prevalence of type 2 diabetes in people with psychosis was observed at 45-54 years of age. The adverse consequences for cardiovascular morbidity and mortality may therefore be most evident after that peak, consistent with previous reports of elevated mortality associated with coronary heart disease relatively early in life (27).

Increasing age, obesity, sedentary lifestyle, family history of diabetes, treated hypertension and treated hypercholesterolemia were all associated with current type 2 diabetes in our sample of people with psychosis. A body mass index of at least 40 and treated hypercholesterolemia were the strongest predictors of current type 2 diabetes after adjustment for all other predictors. Age, male gender (after adjustment for the other risk factors), treated hypertension and family history of diabetes were also associated with an elevated risk in a multivariate model. The 6-fold increased risk of type 2 diabetes in association with treated hypercholesterolemia, 4-fold after adjustment for other predictors, was much higher than the 1.09-fold elevated risk associated with any statin use in the general population in a recent meta-analysis (28).

Obesity has been emphasized as a potent risk factor for diabetes. Reducing body weight is also a major focus of efforts to improve the physical health of those with serious mental illness (29). A body mass index of at least 40 is associated with a 7-fold increased risk of diabetes in the general population (30), while it was associated with a 9-fold increased risk in men with psychosis, and a 14-fold increased risk in women with psychosis.

Individuals with psychosis are known to lead extremely sedentary lives (31), but even a very low level of self-rated recent vigorous activity was associated with a significantly lower risk of current type 2 diabetes before adjustment for other predictors. This is encouraging for those struggling to develop interventions that reconcile national guidelines with self-rated "best" activity levels in those with psychosis. More work needs to be done to identify the minimum level of regular vigorous exercise required to significantly and persistently lower risk for type 2 diabetes in people with psychosis, given other risk factors.

The risk of type 2 diabetes is typically elevated 2- to 4-fold in association with a positive family history, depending on

the strength of that history (32), and this is exactly what we observed in people with psychosis.

Men are at slightly greater risk for type 2 diabetes in the general community (24), but a significant effect of male gender on risk for type 2 diabetes in people with psychosis was not observed until after adjustment for sex differences in the prevalence of other predictors. This underscores the very high prevalence of risk factors among women with psychosis.

Clozapine and olanzapine have been associated with an increased risk for type 2 diabetes (4,33), but the development of type 2 diabetes may also influence which antipsychotic drugs are prescribed over time (34,35). In our cross-sectional observational survey, current treatment with clozapine was associated with an elevated risk, while current treatment with olanzapine was associated with a lower risk, relative to the rest of the sample. Physicians may have taken some of their patients with diabetes or pre-diabetes off olanzapine because they know it is associated with diabetes; that risk has been well publicized. Clozapine is used in Australia only for those who are deemed treatment resistant, and physicians may be unlikely to take their diabetic patients off clozapine, because this is not recommended (36). Current clozapine and olanzapine treatment was not significantly associated with current type 2 diabetes after adjustment for other predictors.

Antipsychotic drug treatment has been shown to be associated with weight gain and adverse changes in blood lipids in experimental studies (37). These changes begin shortly after first exposure to those drugs (38) and accrue over time (39). Some of the risk associated with current body weight and current treated hypercholesterolemia will therefore be attributable to past antipsychotic drug treatment, which we could not model, and some may be due to other causes (e.g., lifestyle, genetics). Only prospective longitudinal studies, from the point of first exposure to antipsychotic drugs, could disentangle these effects over time. We can, however, identify a list of variables that should be examined in such models, and which may also confound some published estimates of the association between antipsychotic drugs and risk for type 2 diabetes: male gender, age, severity of obesity, treated hypercholesterolemia, treated hypertension, family history of diabetes, physical inactivity and psychosis. Static adjusted odds ratios may not do justice to the complexity of the longitudinal inter-relationships among these factors. Further work is required to disentangle the architecture of risk for type 2 diabetes in people with psychosis, and to identify the most fruitful targets for intervention.

Our diagnosis of type 2 diabetes did not include cases defined on the basis of glucose tolerance testing and therefore underestimates the true prevalence of type 2 diabetes. These missing cases are important to identify in future surveys, because they are at greatest risk of early death in the general population (40). Furthermore, our survey did not record birth weight, gestational diabetes or maternal gestational diabetes, and we therefore could not estimate the effect of the intrauterine environment or diabetes in pregnancy on risk. Risk for type 2 diabetes that is associated with low birth weight is exacerbated in those in the general population who experience excess and rapid weight gain in early adulthood, and that weight gain is associated with an earlier onset of type 2 diabetes (14). People with psychosis often experience excess and rapid weight gain in early adulthood in association with the onset of psychosis and antipsychotic drug treatment. The relationship between birth weight, excess and rapid weight gain in early adulthood and consequent risk for early onset type 2 diabetes in people with treated psychosis is unknown but warrants examination.

Current antipsychotic drug treatment does not capture the cumulative effect of all antipsychotic drug use or the associated cumulative dosage effects over a lifetime. Polypharmacy is common and occurs across many different drug classes. Background medication may therefore confound effects that appear to be due to currently prescribed antipsychotic drugs. Identifying an appropriate reference group for antipsychotic drug comparisons is difficult. Some previous studies have used haloperidol (41), but only a handful of our survey participants were being treated with that drug. We therefore elected to compare those taking clozapine or olanzapine with those taking neither, but using a different reference group may generate different findings.

In conclusion, risk factors for type 2 diabetes established in the general population are also common in people with psychosis and strongly associated with current type 2 diabetes in those people. The current study provides large sample evidence that these factors may confound estimated risk associated with antipsychotic drug treatments over time, as others have cautioned (16,17,42). However, we observed very little cross-sectional confounding in a sample diagnosed with psychosis for a mean of 15 years. Patterns of association over the course of psychotic illness for predictors of type 2 diabetes, including antipsychotic drug effects, are likely to be complex. The cross-sectional model reported here should therefore be interpreted cautiously.

A strong focus on weight reduction to reduce adverse physical health outcomes of psychosis is warranted, but effective prevention strategies for type 2 diabetes should be broadened to include targeting those with emerging dyslipidemia, hypertension (43) and positive family histories of diabetes (31,44). Lowering blood pressure is the single most effective intervention to reduce cardiovascular morbidity and mortality in those with type 2 diabetes in the general population (45). An equivalent evidence base to guide us for those with psychosis is not yet available.

Persistent lifestyle changes will likely be required to modify adverse health outcomes associated with type 2 diabetes. Small scale interventions of short duration will not suffice. This is a substantial challenge to current practice in clinical psychiatry. Drug prescriptions may be life-long, but lifestyle interventions are typically non-intensive and short lived. The smallest effects of lifestyle interventions are greeted with enthusiasm (29), but belie the enormity of the changes

actually required to extend and improve the physical health of those with psychosis.

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Psychotic experiences as a predictor of the natural course of suicidal ideation: a Swedish cohort study

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Psychotic experiences are far more prevalent in the population than psychotic disorders and are associated with a wide range of depressive, anxiety and behavioral disorders, as well as increased risk for psychotic disorder. Recently, psychotic experiences have been highlighted as a potentially valuable clinical marker of risk for suicidal behavior. There have been few studies to date, however, to assess psychotic experiences as a predictor of suicidality over time. We wished to assess whether young persons with suicidal ideation at baseline assessment who reported psychotic experiences were at higher risk for persistence of suicidal ideation at follow-up than young persons who also reported suicidal ideation at baseline but who did not report co-occurring psychotic experiences. A total of 2,263 adolescents were assessed at age 13 to 14 years for psychotic experiences, suicidal ideation and internalizing and externalizing psychopathology. Participants were re-assessed at ages 16 to 17 years and 19 to 20 years. Among 13- to 14-year olds with suicidal ideation, co-occurring psychotic experiences did not predict an increased odds of persistence of suicidal ideation to age 16 to 17 years (OR=0.94, 95% CI: 0.19-4.78). Among 16- to 17-year olds with suicidal ideation, however, co-occurring psychotic experiences predicted a 6-fold increased odds of persistence of suicidal ideation to age 19 to 20 years (OR=5.53, 95% CI: 1.33-23.00). Psychotic experiences are an important but under-recognized marker of risk for persistence of suicidal ideation, in particular from mid-adolescence. An increased emphasis on the clinical assessment of psychotic experiences in mental health services should be a priority.

Key words: Psychotic experiences, suicidal ideation, adolescence, cohort study

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Suicidal thoughts and behavior represent major sources of morbidity and mortality worldwide (1,2). There are an estimated one million lives lost by suicide each year (3) and a much larger number of individuals who report suicidal ideation. Although most suicidal ideation is transient and does not require close clinical attention (4), for some individuals, suicidal ideation becomes persistent, causing long-term morbidity, mental distress and ultimately increasing the risk of attempted and completed suicide (5). Identification of individuals whose suicidal ideation is likely to become persistent, however, is a complex challenge in clinical psychiatry. Clinical severity of psychopathology, most notably depression, is a known risk marker for persistence of suicidal ideation (4,6) but, given that symptomatic severity is a continuous measure, it has limited clinical utility in terms of identifying specific individuals as being at "high risk".

Recently, psychotic experiences have emerged in the literature as potentially important markers of risk for suicidality (7-10). As opposed to true psychotic symptoms, psychotic experiences are mainly attenuated in nature; that is, hallucinatory and delusional experiences with intact reality testing. For example, a person may report hearing a voice speaking in the absence of an external stimulus but, unlike in frank psychosis, the individual will usually accept that the voice is, in fact, a product of his/her own mind. Psychotic experiences are far more common in the population than frank psychosis, especially in young people. A meta-analysis of all community studies found that 17% of children and 7.5% of adolescents in the general population report psychotic experiences (11). A meta-analysis of longitudinal studies demonstrated that 7.4% of individuals who report psychotic experiences go on to develop a psychotic illness (12). However, psychotic experiences are associated with a wide variety of mental disorders, not limited to psychosis (13-18). In fact, recent research has found that the majority of community-based individuals with psychotic experiences have at least one non-psychotic Axis I disorder (17), including depressive, anxiety and behavioral disorders.

Recent cross-sectional research has demonstrated a strong association between psychotic experiences and suicidality (7,10,19) and two longitudinal reports have demonstrated high risk of suicide attempts in population samples who report psychotic experiences (9,20). We wished to investigate whether psychotic experiences would act as a risk marker for the persistence of suicidal ideation in a longitudinal study of Swedish adolescents followed to early adulthood, something that has not been addressed in the literature to date. Specifically, we assessed whether young people with suicidal ideation who reported co-occurring psychotic experiences were more likely to also report suicidal ideation at follow-up compared to young people who reported suicidal ideation but did not report psychotic experiences, since this could provide a valuable clinical risk marker to identify individuals at high risk of persistence of suicidal ideation.

METHODS

The study was based on data from the Swedish Twin Study of Child and Adolescent Development (TCHAD) (21). The target sample consisted of all 2,960 twins born in Sweden between May 1985 and December 1986 who were

alive and residing in Sweden in 1994. They were assessed three times via mailed questionnaires: at ages 13 to 14, 16 to 17, and 19 to 20 years. Response rates at different waves were as follows: at ages 13 to 14, parents = 1,063 (73%), children = 2,263 (78%); at ages 16 to 17, parents = 1,067 (74%), children = 2,369 (82%); at ages 19 to 20, parents = 1,158 (78%), children = 1,705 (58%). Attrition did not vary by psychotic symptoms at 16 to 17 year follow-up ($\chi^2<0.01$, $p=0.98$) or 19 to 20 year follow-up ($\chi^2=0.65$, $p=0.42$).

Suicidal ideation was assessed at each time point based on the endorsement of the following item from the Youth Self-Report (YSR, 22) when the participants were aged 13 to 14 and 16 to 17 years, and from the Adult Self-Report (ASR, 23) when the participants were aged 19 to 20 years: "I think about killing myself". There was no information on suicide attempts. Symptoms of psychopathology were also assessed using the YSR/ASR. Internalizing psychopathology (such as depressed mood, anxiety, withdrawn behavior) was self-rated using the internalizing scale of the YSR when the participants were aged 13 to 14 and 16 to 17, and using the ASR when the participants were aged 19 to 20. Externalizing psychopathology (such as attention problems, hyperactivity, antisocial behavior) was parent-rated using the externalizing scale of the Child Behavior Checklist (CBCL, 22) when the participants were aged 13 to 14 and 16 to 17, and using the Adult Behavior Checklist (ABCL, 23) when the participants were aged 19 to 20. The YSR, ASR, CBCL and ABCL are standardized questionnaires for parents and children to rate the children's frequency and intensity of emotional and behavioral problems exhibited in the past 6 months. The psychometric properties of these scales have been examined in both population-based and clinical samples, presenting good reliability, as well as convergent and discriminative validity (22,23). All items were scored on a 3-point scale (0 = not true; 1 = sometimes true; and 2 = often true). The YSR is based on self-ratings but consists of the same items as those in the CBCL. The ABCL and ASR consist of similar or developmentally appropriate counterparts of items used in CBCL and YSR. Total scores were calculated at each time point for internalizing and externalizing problems and these were controlled for in our analyses of the relationship between suicidal ideation and psychotic experiences.

Psychotic experiences were assessed at each time point using the following item from the YSR/ASR: "I hear sounds or voices that other people think aren't there". This item has previously been shown to have good positive and negative predictive value for clinically verifiable psychotic experiences (24). In a community survey of adolescents, the item not only detected young people with auditory hallucinations (compared to clinical-interview verified auditory hallucinations, positive predictive value 71%, negative predictive value 90%), but psychotic experiences in general (frank and attenuated hallucinations and delusions) (positive predictive value 100%, negative predictive value 88%) (24). Therefore, this item was specifically selected to assess for psychotic experiences in our sample at all three time points.

Selective attrition of participants with psychotic experiences was tested using chi squares. We report the prevalence of psychotic experiences and suicidal ideation at each assessment point. We used logistic regression to assess whether individuals with suicidal ideation at age 13 to 14 years who reported psychotic experiences were more likely to have persistent suicidal ideation at age 16 to 17 years follow-up, controlling for internalizing and externalizing psychopathology. We then repeated this analysis for individuals with suicidal ideation at age 16 to 17 years who reported psychotic experiences compared to those who did not report co-occurring psychotic experiences. Analyses were controlled for sex and for cannabis use. A robust sandwich estimator was used to account for potential clustering as a result of the use of twin data.

RESULTS

Suicidal ideation was reported by 116 among 13- to 14-year olds (5%), 191 among 16- to 17-year olds (8%) and 138 among 19- to 20-year olds (8%). Thirty five percent of 13- to 14-year olds who reported suicidal ideation had persistent suicidal ideation at age 16 to 17 years, and 29% of 16- to 17-year olds who reported suicidal ideation had persistent suicidal ideation at age 19 to 20 years (Table 1).

Psychotic experiences were reported by 162 among 13- to 14-year olds (7.3%), 89 among 16- to 17-year olds (3.9%) and 44 among 19- to 20-year olds (2.6%). Sixteen percent of 13- to 14-year olds who reported psychotic experiences had persistent psychotic experiences at age 16 to 17 years. Nineteen percent of 16- to 17-year olds who reported psychotic experiences had persistent psychotic experiences at age 19 to 20 years.

Internalizing and externalizing psychopathology scores at age 13 to 14 years predicted psychotic experiences at age 16 to 17 years (respectively, OR=1.08, CI 95%: 1.05-1.11; OR=1.06, CI 95%: 1.03-1.10). Internalizing and externalizing psychopathology scores at age 16 to 17 years predicted psychotic experiences at age 19 to 20 years (respectively,

Table 1 Baseline suicidal ideation and risk for suicidal ideation at follow-up assessment

		Suicidal ideation at follow-up			
	N	N	%	OR	95% CI
Suicidal ideation at 13 to 14 years	116	37	34.9	4.17	2.80-6.20
Suicidal ideation at 16 to 17 years	191	42	29.4	3.90	2.78-5.46

Follow-up for 13- to 14-year olds was at age 16 to 17 years; follow-up for 16- to 17-year olds was at age 19 to 20 years

Table 2 Risk for suicidal ideation at follow-up assessment in adolescents with baseline suicidal ideation with or without psychotic experiences

		Without psychotic experiences		With psychotic experiences			
	N	N	% with suicidal ideation at follow-up	N	% with suicidal ideation at follow-up	OR	95% CI
Suicidal ideation at 13 to 14 years	109	88	31%	21	29%	0.94	0.19-4.78
Suicidal ideation at 16 to 17 years	179	156	27%	23	54%	5.53	1.33-23.00

Follow-up for 13- to 14-year olds was at age 16 to 17 years; follow-up for 16- to 17-year olds was at age 19 to 20 years
Analyses were controlled for sex, internalizing and externalizing psychopathology scores and cannabis use

OR=1.09, CI 95%:1.06-1.13; OR=1.04, CI 95%:1.00-1.08). There was a non-significant trend for cannabis use at age 13 to 14 years to predict psychotic experiences at age 16 to 17 years (OR=1.28, CI 95%: 0.69-2.40). Cannabis use at age 16 to 17 years predicted psychotic experiences at age 19 to 20 years (OR=3.79, CI 95%: 1.45-9.87). We controlled for internalizing and externalizing psychopathology, for cannabis use and for sex in the subsequent analyses on the relationship between psychotic experiences and suicidality (below).

Among adolescents with suicidal ideation at age 13 to 14 years, co-occurring psychotic experiences did not predict an increased odds of persistence of suicidal ideation to age 16 to 17 years (see Table 2). Among adolescents with suicidal ideation at age 16 to 17 years, however, co-occurring psychotic experiences predicted a 6-fold increased odds of persistence of suicidal ideation to age 19 to 20 years. In fact, while 27% of 16- to 17-year olds with suicidal ideation but who did not report psychotic experiences had persistent suicidal ideation at age 19 to 20 years, more than half (54%) of 16- to 17-year olds with suicidal ideation and who also reported co-occurring psychotic experiences had persistent suicidal ideation at age 19 to 20 years (see Table 2).

DISCUSSION

In a longitudinal study of a community adolescent sample, we found that psychotic experiences were a strong marker of risk for persistence of suicidal ideation from mid adolescence to late adolescence/early adulthood. This was the case even after controlling for internalizing and externalizing psychopathology and for cannabis use. Psychotic experiences in early adolescence (age 13 to 14 years) did not predict an increased risk for persistence of suicidal ideation to mid adolescence. This is consistent with research demonstrating that psychotic experiences are more closely associated with severe psychopathology from mid adolescence onward compared to childhood and early adolescence (17). In early adolescence, then, psychotic experiences may be less informative about risk for suicidal behavior than is the case from mid adolescence. It is also possible that younger adolescents are more likely to misinterpret questions on psychotic experiences, although previous research has shown that the item used in the current research is generally well understood even from early adolescence (24).

While it is well recognized that frank psychotic symptoms are associated with higher risk for suicidal behavior, for example in the case of major depressive disorder with psychotic features, the results of the current study demonstrate that a much broader and more prevalent class of (attenuated) psychotic experiences also mark high risk for suicidality. Suicidal ideation among 16- to 17-year olds persisted to age 19 to 20 years for just a minority (27%) of those who did not report psychotic experiences. However, suicidal ideation persisted to age 19 to 20 years for the majority (54%) of 16- to 17-year olds who reported co-occurring psychotic experiences.

There are a number of reasons why psychotic experiences may act as a marker of increased risk for suicidal behavior. Several risk factors for psychotic experiences have also been independently demonstrated in cohorts with suicidal behavior (25-29). Notably, psychotic experiences are associated with the presence of multiple comorbid Axis I diagnoses (multimorbidity) (17,19), an established risk factor for suicidal behavior (25). With regard to Axis II psychopathology, however, it is important to note that, even in clinical samples, only a very small minority of individuals with psychotic experiences have (or go on to develop) borderline personality disorder (18). In terms of other risk factors, young people with psychotic experiences have been shown to have poorer global/socio-occupational functioning, even compared to other young people with psychopathology but who do not report psychotic experiences (19), and to have neurocognitive deficits in processing speed in particular (30,31), the most replicated cognitive deficit in individuals with suicidal behavior (26). Psychotic experiences have also been shown to have a strong relationship with childhood trauma, such as physical and sexual abuse, bullying and exposure to domestic violence (32-41). Other research has shown that individuals who report psychotic experiences have increased sensitivity to stress (42) and poorer coping skills (43,44), factors that might also contribute to risk for suicidality in the context of life stressors. Emerging neuroimaging research is also demonstrating interesting overlap between these groups, including volumetric differences in

the cingulum and orbitofrontal cortex in young people with psychotic experiences (45), two centers known to be important in stress regulation (46) and which have been highlighted in imaging studies of individuals with suicidal behavior (47). Furthermore, recent biomarker research has demonstrated important overlaps between markers for suicidality and psychosis (48).

A strength of the current study is its longitudinal nature. We were also able to assess, for the first time, the relationship between suicidal ideation and psychotic experiences through early to late adolescence and into early adulthood. A limitation is that, while the data allowed us to look at risk for later suicidal ideation, we were not able to identify who in this group had clear suicide intent or suicide attempts; however, persistent suicidal ideation, and the long-term psychological distress associated with it, are important outcomes in their own right in addition to the importance of deaths from suicide. Although our sample was relatively large, subgroup analyses involved relatively small groups and, because of this, confidence intervals were wide. Response rates were good for both young people and parents at ages 13 to 14 years and 16 to 17 years, but were lower than desirable among young people at age 19 to 20 years (58% of young people versus 78% of parents); however, participation did not vary by psychotic experiences.

In conclusion, we found in a longitudinal study that psychotic experiences were a strong clinical risk marker for the persistence of suicidal ideation from mid-adolescence into late adolescence and early adulthood. This finding was not explained by internalizing or externalizing psychopathology or by cannabis use. These results highlight the need for an increased emphasis on the clinical assessment of (attenuated and frank) psychotic experiences in mental health services: the presence of psychotic experiences should alert the clinician that suicidal ideation is unlikely to be transient. In the current research, suicidal ideation was still present 3 years later in the majority of 16- to 17-year olds with suicidal ideation who reported co-occurring psychotic experiences. Given the public health importance of suicidal behavior worldwide, further research to develop our understanding of this relationship, and the mechanisms that underlie it, should be a priority.

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Markers of inflammation in schizophrenia: association vs. causation

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Inflammation is a complex response of the host to tissue injury, such as infection or physical insult (1). The main role of inflammation is to quickly eliminate pathogens by initiating an adaptive immune response through stimulation of antigen-specific T- and B-lymphocytes and their regulating immune-transmitters, the pro-inflammatory cytokines. Cytokines are divided into predominantly pro-inflammatory and predominantly anti-inflammatory types (2). Pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), are secreted by monocytes and macrophages and activate other cellular components of the inflammatory response. Anti-inflammatory cytokines, such as interleukin-4 (IL-4), help to down-regulate the inflammatory immune response.

The role of inflammation in schizophrenia has received intense attention and a cytokine-mediated mechanism represents the keystone of a number of hypotheses formulated in the past two decades (2-4). The macrophage T-lymphocyte hypothesis postulates that chronically activated macrophages produce cytokines, such as interleukin-1 (IL-1), interleukin-2 (IL-2), tumor necrosis factors, interferon-alpha and interferon-gamma (5). The "T helper hypothesis" advances the idea of a shift away from cytotoxic cell immune function toward humoral immune reactivity (6). The microglia hypothesis argues that pro-inflammatory cytokines and free radicals are released by activated central nervous system microglia, causing abnormal neurogenesis, neural degradation and white matter abnormalities, which are known to play a role in the pathogenesis of schizophrenia (7). A convergence between neuroinflammatory changes and dopamine and glutamate receptors has also been postulated, and clinical trials with biological therapies developed for the reduction of inflammation (8,9) and for autoimmune disorders (10,11) are seriously considered.

The significance of cytokine abnormalities and other markers of immune dysfunction identified in patients with schizophrenia can be examined through the prism of Bradford Hill's guidelines (12), a widely accepted model for judging whether an association can contribute to cause a pathological phenomenon. Based on this framework, we evaluate here the *strength* of the association; its *consistency* in studies performed by different investigators on different samples; its *temporality*, by trying to determine whether the inflammation has preceded the onset of schizophrenia; its *biological gradient*, meaning that the severity of schizophrenia should correlate with the magnitude of the inflammatory process; its *plausibility* as a pathophysiological mechanism; the *coherence* between epidemiological and laboratory findings; and the *specificity* of inflammatory abnormalities.

STRENGTH AND CONSISTENCY

A thorough review of 40 studies of cytokine alterations in schizophrenia has indicated substantial inter-observer agreement with regard to the magnitude of increase in the levels of IL-6, soluble IL-2 receptor and TNF-alpha in first-episode psychosis and acutely relapsed inpatients compared to healthy controls (3). For example, effect sizes in drug-naïve, first-episode patients were 0.81 for TNF-alpha, 1.03 for the soluble IL-2 receptor and 1.40 for IL-6. Other cytokines (IL-1 beta, transforming growth factor-beta, interferon-gamma and IL-12) had somewhat lower effect sizes.

TEMPORALITY

Cytokine levels and other biomarkers of inflammation have not been longitudinally assessed prior to the clinical recognition of schizophrenia. Therefore, there is no direct proof for a premorbid pathological phenotype. A temporal correlation has been suggested in a few small scale studies, which have shown abnormal levels of interferon-gamma (13), soluble IL-2 receptor (14,15) and IL-6, and TNF-alpha elevations (15) in patients with schizophrenia and, to a lower extent, in their relatives compared to healthy controls.

BIOLOGICAL GRADIENT

A biological gradient correlating levels of pro-inflammatory cytokines and severity of schizophrenia has not been convincingly demonstrated. The correlation between the

cytokines IL-1 beta, IL-6, IL-9, and TNF-beta with Positive and Negative Syndrome Scale (PANSS) total and positive scores identified in a cross-sectional study became insignificant after correcting for multiple comparisons, and no correlation was found with the negative symptoms subscale scores (16).

The trajectories of cytokine levels after treatment appear to be different in first-episode psychosis as compared to schizophrenia in relapse (17). Meta-analytic data show that the levels of some cytokines (IL-6, IL-1 beta, and transforming growth factor-beta) return to normal after antipsychotic treatment, while the levels of others (TNF-alpha, soluble IL-2 receptor, IL-12) remain elevated after the symptoms of an acute exacerbation are controlled (3). This heterogeneity has been interpreted to indicate that levels of different cytokines may be either trait or state markers (3). The construct has not been proven to have specificity for schizophrenia, but rather for psychotic features (18).

Longitudinal studies of blood auto-antibodies in schizophrenia have also failed to indicate a biological gradient. The proportion of patients with positive titers for anti-cardiolipin antibodies measured at the time of an acute illness exacerbation and again after improvement following antipsychotic drug treatment were 19.3% vs. 23.8% ($p=0.62$) for IgG and 15.8% vs. 26.2% ($p=0.22$) for IgM, and titers were negatively correlated with the PANSS positive subscale scores (19).

PLAUSIBILITY

This potential attribute can be inferred from trials of anti-inflammatory drugs as adjunctive therapies in schizophrenia.

In a recent meta-analysis of cyclo-oxygenase-2 inhibitors and aspirin given adjunctively with antipsychotic drugs, including 8 studies ($N=774$ patients), the mean effect size for the PANSS positive subscale scores was -0.189 and the upper limit of the 95% confidence interval was -0.005, suggesting that the outcome of the intervention for this type of symptoms was minimal/small (8). Moreover, the mean effect sizes for PANSS total and negative symptoms scores were non-significant.

A meta-regression analysis of the data indicated an inverse relationship between the severity of negative symptoms at baseline and the efficacy of treatment with non-steroidal anti-inflammatory drugs, a finding that argues for the absence of a biological gradient and reduces even further the plausibility of a role for inflammation in determining the severity of schizophrenia. Nevertheless, effect sizes for total PANSS scores were larger in trials of aspirin and in studies with more first-episode patients (8).

Another recent exploratory meta-analysis found that estrogens and N-acetyl cysteine had small to moderate effect sizes when added to antipsychotics for PANSS total symptoms (9).

COHERENCE

From an epidemiological standpoint, the relationship between inflammation and schizophrenia has been investigated only in Denmark, in a nationwide study on the risk of autoimmune disease in individuals with a personal or family history of schizophrenia (20).

The incidence rate ratios indicated an association between schizophrenia and relatively infrequent conditions, such as autoimmune hepatitis, Guillain-Barré syndrome, multiple sclerosis, primary biliary cirrhosis, and pernicious anemia. On the other hand, the incidence of schizophrenia was lower than expected among patients with more common and undisputedly autoimmune conditions, such as seropositive rheumatoid arthritis, polymyalgia rheumatica, ankylosing spondylitis and autoimmune thyroiditis. The incidence rate ratio for seropositive rheumatoid arthritis at the onset of psychotic disorder was 0.75 and decreased to 0.60 five years later.

In the same study, some results are at odds with a clear relationship between inflammation and schizophrenia. For example, schizophrenia was found to be more frequently present in people with Crohn's disease compared to the general population, while at the same time being substantially less frequent in those with ulcerative colitis (20).

SPECIFICITY

There is no evidence for specificity of elevated pro-inflammatory cytokines or auto-antibodies, as similar findings have been observed in other psychiatric disorders.

Pro-inflammatory markers are strongly and consistently associated with depression. For example, in a meta-analysis of 25 studies of clinically depressed patients and healthy controls, the effect size of IL-6 was 0.71, and the 95% confidence interval ranged from 0.46 to 0.97 (21). The association remained significant after correction for comorbid somatic disorders that could correlate with immune dysfunction, such as cancer, and for treatment with antidepressant drugs, which may reduce the release of pro-inflammatory cytokines from activated microglia (22).

An expanded survey confirmed the significantly higher concentrations of IL-6 and TNF-alpha in depressed patients compared to healthy controls, and the effect size did not appear to be influenced by the type of ELISA assay used (23).

Recent data also indicate that treatment with antidepressants reduces the levels of biomarkers of inflammation (24). There is also evidence, generated in four placebo-controlled trials, that treatment with the anti-inflammatory drug celecoxib, a cyclo-oxygenase-2 inhibitor, leads to greater mean reductions in the Hamilton Rating Scale for Depression and to significantly higher remission rates than placebo (25).

Increased levels of pro-inflammatory cytokines have been shown to correlate with the severity of depression, and

levels of IL-6 and TNF-alpha were higher in depressed patients with suicidal ideation or attempts (26).

However, in random effects and fixed effects meta-analytic models, the improvement of depressive symptoms did not correlate with a change in serum levels of TNF-alpha, and the biological gradient of IL-6 was very small (27). Subgroup analyses suggested that, in contrast to other classes of antidepressant drugs, serotonin reuptake inhibitors may decrease TNF-alpha and IL-6 levels, but such effects did not influence the proportion of patients achieving a 50% reduction in depressive symptoms.

The plausibility and coherence of these findings have remained relatively weak. For instance, although clinically depressed patients have a higher expression of autoimmune abnormalities, as reflected in the titers of anti-phospholipid antibodies, there is a much lower incidence of positive patients than in systemic lupus erythematosus, a classical autoimmune disorder (28). Age and gender may be stronger determinants of the titers of auto-antibodies than the type of affective disorder, affective state or psychotropic medication (29). On the other hand, in contrast with schizophrenia, the development of depression-like behavior can be studied in experimental models and has been shown to be related to a cell-mediated immune response (30).

Cytokine alterations similar to those found in schizophrenia have also been identified in patients with bipolar disorder. A meta-analysis of 30 studies has found significant elevations of IL-6, soluble IL-2 receptor and TNF-alpha in bipolar patients compared to healthy controls (31). For IL-6, the difference was primarily due to the immune changes present during acute mania, as levels were normal in bipolar depressed and euthymic patients. The levels of TNF-alpha were similarly elevated in manic and depressed patients, and a biological gradient, i.e., normalization during periods of euthymia, was not observed.

SUMMARY AND CONCLUSIONS

The application of Bradford Hill's criteria for distinguishing association from causation with regard to increased pro-inflammatory cytokines in schizophrenia finds robust evidence for *strength* and *consistency*. However, a *biological gradient* has not been convincingly demonstrated and there is no direct proof of *temporality*. Fulfillment of the criteria for *plausibility* and *coherence* is modest, at best. Most importantly, the association lacks *specificity*, because similar or stronger correlations have been reported in major depression and bipolar disorder.

We believe that the explanatory paradigm should be changed from a strong emphasis on causal role of inflammation in schizophrenia to the recognition that the observed immune dysfunction may be related to other factors, such as obesity and psychological stress. Visceral fat depots (32) and adipocyte hypertrophy (33) have been linked to a higher degree of inflammation. It has been observed that, whilst adipose tissue from lean individuals may preferentially secrete anti-inflammatory adipokines (including adiponectin, IL-10, IL-4 and IL-13), obesity is associated with increased levels of pro-inflammatory cytokines (such as TNF-alpha, leptin, plasminogen activator inhibitor, IL-6, IL-1 beta) (34), coupled with a reduction in the secretion of anti-inflammatory adipokines (35-39). Moreover, psychological stress may activate inflammatory responses in the brain (40). Both chronic and acute stress have been associated with increased production of pro-inflammatory cytokines, including IL-6 and C-reactive protein (41), and decreased levels of anti-inflammatory ones (42).

Overall, the review of currently available data suggests that there is insufficient evidence that the replicated, strong association between schizophrenia and elevated inflammatory markers has etiopathological relevance. Future studies need to follow patients from the attenuated psychosis syndrome to full-blown schizophrenia, and measure inflammatory cytokine levels in those patients who convert to psychosis and those who do not.

Since inflammation might be triggered by many factors, including weight gain/obesity and psychological stress, both cross-sectional and longitudinal studies of pro-inflammatory cytokine levels in schizophrenia need to control for these factors. Such studies should investigate the possibility that non-specific inflammatory changes may influence the expression of psychosis and other severe mental disorders.

Should such inflammatory triggering of psychopathology occur, at least in subgroups of patients or in specific phases of the illness, the finding could clearly lead to novel treatment approaches.

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The first two authors contributed equally to this work.

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Management of obesity in the psychiatrist's office

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Obesity is an epidemic in the developed countries, and the rest of the world is quickly catching up. Patients with severe mental illness (SMI) suffer from two to three times higher rates of obesity (1), and this has translated into much higher rates of obesity-related morbidity and premature mortality in this population (2). This raises the question if obesity management should be added to the expanding responsibilities of psychiatrists. Our answer to this question is a resounding "Yes".

First, obesity is a behavioral problem that involves eating too much and moving too little. The most robust evidence for effective management of obesity is for behavioral interventions, usually referred to as lifestyle interventions. These are typically based on principles of cognitive behavioral therapy and social cognitive change. Psychiatrists are experts of behavioral change and are equipped with the tools to employ against this disease.

Second, it has become abundantly clear that psychiatric medications, especially antipsychotics, play an important role in the increased rates of obesity among patients with SMI (3). While it is preferable to prevent the excess weight gain due to psychotropic medications, this is not always possible. Many patients will already be overweight or obese at the initial visit to a psychiatrist. Management of overweight and obesity is therefore as much a part of psychiatrists' duty as the management of other medication side effects, ranging from movement disorders to impaired sexual function. Obesity is also associated with increased rates of depression, decreased quality of life, and increased stigma in this population. Obesity is a calamity that needs to be managed in the psychiatrist's office.

OBESITY AS A MEDICATION SIDE EFFECT

The first task of weight management is not to exacerbate the problem through medication side effects. There is abundant evidence that switching from a weight-inducing medication to one that has lower weight gain liability or is weight neutral can produce clinically significant weight loss. A switch should be considered for any patient who is obese or who has gained a clinically significant amount of weight (>5% of body weight), or who has other evidence of severe metabolic dysfunction (e.g., poor diabetes disease control). Such switching between antipsychotic medications can result in weight loss of 2-3 kg after 24 weeks, and also clinically significant changes in non-high-density lipoprotein (non-HDL) cholesterol, triglyceride and glucose levels. In the context of close clinical monitoring, switching can be tolerated without increased risk of psychiatric hospitalization or significant psychiatric symptom exacerbation (4).

There are several straightforward principles of management of the side effect of weight gain. Any medication that blocks central histamine-1 (H1) receptors can increase appetite and produce weight gain. Such medications include the antipsychotics olanzapine and quetiapine; the antidepressants mirtazapine and several older tricyclic antidepressants; and central antihistamines that are used to treat anxiety, such as hydroxyzine. These medications should be avoided as initial treatments, or switched to alternatives with lower weight gain liability whenever possible. Many of these medications also block serotonin 2c (5HT2c) receptors, which also induces appetite (though to a lesser extent than H1 blockade). This may explain why some second-generation antipsychotics which are not antihistaminic may cause significant weight gain in some patients.

Dopamine-2 (D2) receptor blockade has also been associated with significant weight gain, especially among treatment-naïve patients presenting with a first episode of psychosis (5). Since all antipsychotic medications in current use are D2 blockers, it is essentially impossible to avoid D2 blockade when prescribing pharmacotherapy to patients with schizophrenia and other psychotic disorders. However, newer antipsychotic agents are increasingly used for augmentation or as first line medications in the treatment of bipolar disorder and other mood disorders. There are more weight neutral strategies for treatment of these conditions, and such options should be tried first, especially among patients who are already overweight. Mood stabilizers such as lithium and valproate, although weight inducing themselves through unknown mechanisms, are associated with less weight gain than antipsychotic agents. Many newer antidepressants are weight neutral, or may even be associated with weight loss, as in the case of bupropion.

LIFESTYLE MODIFICATION

Weight loss through a healthy lifestyle (increased physical activity and decreased caloric intake) can prevent or delay the onset of type 2 diabetes and cardiovascular disease, particularly among high-risk individuals. Even small reductions in body weight can lead to substantial improvements in a metabolic risk profile: weight loss of as little as 5% of initial body weight can prevent or delay the onset of diabetes, hypertension, hyperlipidemia, and cardiovascular disease (6).

Routine weight monitoring provides the opportunity for psychiatrists to counsel patients about nutrition and physical activity. Scales are available around the world and are a cheap tool that should be a mainstay in every psychiatrist's office. Several minutes of every psychiatric visit should be reserved for weighing the patient, which is itself an effective weight loss tool. Patients (and their families) should be educated about healthy lifestyles. This education does not need to be administered by a nutritionist or other specialist; it can effectively be provided by mental health clinic staff. Brief counseling by primary care clinicians can lead to changes in patient health behaviors (e.g., increased exercise or vegetable consumption) (7). Similar risk assessment and brief advice about behavioral risk should be incorporated into routine psychiatric practice. The patient's nutritional status and previous weight loss efforts should be reviewed. Suggestions should be offered at every visit, and might include: a) identifying one high calorie dietary component such as a sugared beverages or fried chicken, and suggesting healthier alternatives (diet soda or baked chicken); b) incorporating increased physical activity into daily routine, such as taking stairs instead of elevators, or walking to work; c) alerting patients against non-hunger related calorie intake, such as snacking or emotional eating or eating in response to stress; d) stimulus reduction, such as storing high calorie foods out of sight and out of reach.

An obesity medication should not be started without first trying a structured lifestyle program, and lifestyle programs need to be continued after any obesity medication is started. Manualized lifestyle interventions, such as the Diabetes Prevention Program, have substantial evidence of effectiveness in promoting weight loss and can be delivered in community settings by lay persons (8). Such interventions have been adapted for patients with SMI, and several large randomized controlled trials have demonstrated their efficacy (9). At least seven interventions are ready for implementation, but to date, they have not been widely disseminated. As up to 40% of participants can lose a clinically significant amount of weight (5% of baseline weight) through participation in such programs (10), their implementation may represent a tremendous return on a small investment for public mental health agencies. These evidence-based interventions to promote weight loss and decrease diabetes risk must be made available at community mental health centers.

PHARMACOTHERAPY

Among individuals who are not able to lose or sustain sufficient weight loss to improve health with lifestyle interventions alone, adjunctive pharmacotherapy can help (11). But pharmacotherapy options for weight loss for persons with schizophrenia or other psychotic disorders are very limited. Orlistat (a pancreatic lipase inhibitor) blocks fat absorption in the intestines but does not appear to be effective among patients with schizophrenia. Sympathomimetics (diethylpropion and phenteramine) are associated with a risk for psychosis exacerbation, and are relatively contraindicated. The use of topiramate, an anti-seizure medication that has been associated with weight loss when used in patients with schizophrenia, may be limited by the neurocognitive side effects and the risk of metabolic acidosis.

The safety and efficacy of promising newer agents (lorcaserin and the combination of naltrexone and bupropion) among patients with schizophrenia are unknown (12). Lorcaserin, a 5-HT2c agonist, is marketed with a warning for neuroleptic malignant syndrome and serotonin syndrome when used in combination with psychotropic medications, although no such cases have been reported in the literature to date.

The medication with the strongest evidence for diminishing the adverse effects of obesity among patients with schizophrenia is metformin, a medication without a Food and Drug Administration (FDA) indication for weight loss. Like with lifestyle interventions and antipsychotic switching, typical weight loss with metformin is 3 kg at 16 weeks, which is relatively modest and similar to its effect for non-psychiatric patients (13). Metformin, however, also reduces other risk factors for cardiovascular disease, such as triglyceride levels, and may prevent or delay the onset of type 2 diabetes.

Given that metformin appears to be well tolerated by most patients, it should be considered for clinically stable overweight outpatients with schizophrenia or schizoaffective disorder, titrated up to 1000 mg twice daily if tolerated. There are factors that limit its widespread use, however. Care must be taken to minimize the risk of lactic acidosis, and metformin should not be prescribed to patients at increased risk: those with congestive heart failure, renal impairment, hepatic disease, or current alcohol abuse or dependence. Second, treatment duration has not been well defined. FDA labels recommend discontinuation of lorcaserin or phenteramine plus topiramate after 12 weeks if the threshold of less than 5% weight loss is not met, so this might guide the management of metformin. But patients may need longer treatment (than the 16-24 weeks of typical clinical trials) if they do have an initial weight loss. Concerns have been raised recently, however, about the risks of metformin use over longer periods. The evidence suggesting that its chronic use increases the risk of Alzheimer's disease (14) suggests that more work is needed to define an algorithm for weighing this risk with that of cardiovascular disease in any individual or subgroup of patients.

BARIATRIC SURGERY

Bariatric surgery is indicated for patients with severe obesity (body mass index $\geq$ 40 kg/m^2) or medically complicated moderate obesity (body mass index $\geq$ 35-39.9 kg/m^2) and who fail lifestyle and pharmacologic intervention. Long-term studies show that the procedures result in significant weight loss (more than 50% of baseline body weight),

recovery from diabetes, improvement in cardiovascular risk factors, and a 23% reduction in mortality (15).

The limited data about the efficacy and tolerability of bariatric surgery among patients with SMI suggest that outcomes are comparable to individuals without SMI (16). Psychiatrists need to understand how (and when) to advocate for their patients to be considered as surgical candidates. We often know our patients better than any other medical providers, and are in the best position to assess motivation, adherence, and the impact of psychiatric illness on the ability to sustain complex self-care regimens. Moreover, we can provide longer-term follow-up for monitoring of psychiatric symptoms that might emerge after the immediate post-operative period and surgical follow-up.

CONCLUSIONS

Persons with SMI represent a health disparities population with respect to obesity and other cardiovascular risk factors. Obesity represents the obvious starting point for an expansion of the scope of practice of psychiatrists to address these health disparities, given the ease of monitoring outcomes (weight and body mass index), the availability of effective treatments, and the large potential impact on outcomes of changing health behaviors.

Obesity is a chronic illness. Even among patients who lose weight, long-term weight maintenance is difficult. Weight regain is the norm, even with continued lifestyle modification. There is a need for constant vigilance to sustain behavior changes in the face of environmental pressures to regain weight. Patients with SMI may additionally face biologic factors that increase weight regain, including second-generation antipsychotic medications. Psychiatrists need to do more than acknowledge the poor health outcomes among these vulnerable patients; they need to work actively to prevent and address them.

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The RDoC framework: continuing commentary

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We are grateful for the thoughtful comments received in response to the target article about the National Institute of Mental Health (NIMH)'s Research Domain Criteria (RDoC) project that appeared in the February 2014 issue of *World Psychiatry* (1), and appreciate the opportunity to respond briefly to the major themes running throughout the thirteen commentaries (with apologies that space limitations preclude consideration of many interesting points).

We start by clarifying several aspects where we believe that we are in fundamental agreement with the commentators. First, although RDoC was seen by some as a radical departure from current research, we view the project as emerging from a rich history of translational research in brain-behavior relationships and dimensional approaches to psychopathology (e.g., 2). Thus, efforts to introduce biological and quantified behavioral/psychological criteria into diagnostics would not change many time-honored approaches.

We agree that a careful clinical interview is an essential component of the diagnostic process, which would be augmented (not replaced) by neurobiological or behavioral tests. Similarly, we agree with the necessity of studying clinical course and outcome with respect to RDoC domains and constructs. We are also in accord with the need to map RDoC dimensions to etiological factors of various sorts, e.g., such aspects as prenatal conditions and a full range of environmental variables related both to risk and resilience (in fact, as other commentators noted, such etiological studies are an emphasis in RDoC).

Multiple commentators noted the need to characterize the numbers of patients with DSM/ICD disorders that are included in RDoC-themed studies, and we agree that this will be a useful step to maintain crosswalks to the DSM/ICD system (while noting that many participants will not reach traditional diagnostic levels due to the dimensional approach). Finally, we agree that the ultimate arbiter of clinical utility for RDoC – as with any nosology – will be its ability to guide clinicians to personalized (or stratified) treatments that have greater aggregate effectiveness.

In this regard, several commentators expressed different variations of a critical theme that the RDoC framework might contribute in the future, but cannot inform clinical practice at the current time. We agree: RDoC is not intended as a near-term replacement for the ICD/DSM. However, other comments implied that necessary advances in future diagnostics and treatment will naturally eventuate if the current *status quo* for conducting research is maintained. Here, we disagree. Rapidly emerging neurobiological and behavioral data increasingly indicate that future needs cannot be met – or will be very considerably delayed – if the difficult research to align diagnosis with empirical data is not initiated now.

Another aspect of this theme stems from concerns that a future-oriented research project like RDoC slights the pressing needs for research and care of patients at the current time. Two related points may be noted in response to this concern. First, NIMH (like any agency that funds disorder-related research) must balance its resources among support for basic research, translational research, and services/dissemination research; RDoC only concerns the second of these areas, and support for the other areas has not changed – e.g., the NIMH RAISE project (www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml) is a large-scale effort to develop best practices for detection and treatment of first-episode psychosis. Second, the needs for greatly expanded mental health services are all too apparent given the increasing burden of disability due to mental disorders (e.g., 3), and the availability of treatments for mental disorders is well recognized; our view is that research to accelerate enhanced diagnosis and treatment will encourage, rather than discourage, efforts to develop improved mental services in the US and around the world.

Several commentators indicated that RDoC ignores the psyche, subjective experience, or the clinical presentations of disorders – coupled with the related point that RDoC is excessively reductionistic. We would respond that the introduction of neuroscience and modern psychometrics into diagnosis does not mean that the patient's subjective experience or presenting symptoms are unimportant; as pointed out originally (and above), relating the various neurobiological and behavioral measures to symptoms and presenting phenomenology represents an important task in the RDoC scheme. However, we would disagree with a view that the patient's subjective experience, as such, ought to represent the sole or predominant focus of assessment and treatment. We acknowledge that some important clinical phenomena are as yet minimally represented in RDoC; this reflects a considered decision to start with relatively well-established areas of brain-behavior relationships, so as to establish a solid foundation upon which to build toward such poorly understood aspects of psychopathology.

Finally, it should be noted that pre-emption and prevention of disorders constitutes a major long-term objective of the RDoC process. It is now well known that, across many mental as well as neurological disorders, overt dysfunction appears only as a late stage in an ongoing disease process – badly hampering efforts toward early prevention. For mental

disorders, we are now only beginning to target early stages of illness, largely through incipient signs and symptoms as in the schizophrenia prodrome (4). In the future, indicated pre-emption of disorders will require the ability to intervene (e.g., with neuroplasticity interventions and/or targeted neuroprotective compounds) before any symptoms appear. In this context, measures such as functional gene group assays, sensitive cognitive tests, and endophenotypic measures (e.g., event-related potentials) do not constitute a reductionistic approach as such, but rather represent the necessary assessments that would be required for successful risk detection and pre-emption.

We close by repeating our appreciation for the opportunity to continue the discussion by clarifying some points of misunderstanding and acknowledging clear differences of opinion that demarcate the RDoC framework from current approaches to diagnosis. Interested readers are encouraged to visit the RDoC website (www.nimh.nih.gov/research-priorities/rdoc/index.shtml) for more information and links to papers with more extensive descriptions of various aspects of the project.

Appendix

The members of the NIMH RDoC Workgroup are: Bruce Cuthbert (chair), Rebecca Steiner Garcia, Marjorie Garvey, Marlene Guzman, Robert Heinssen, Michael Kozak, Sarah Morris, Daniel Pine, Kevin Quinn, Charles Sanislow, Janine Simmons, and Philip Wang.

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Global priorities of civil society for mental health services: findings from a 53 country survey

Mental disorders account for 13% of global disease burden, and major depression alone is expected to be the largest burden contributor by 2030 (1). For people with mental disorders, life expectancy is reduced by 15-20 years (2). Mental disorders are predicted by 2030 to account for nearly a third of the projected US$47 trillion incurred by all non-communicable diseases (3). They also incur political costs – mental disorders impact on progress towards Millennium Development Goals (4).

Services for people with mental disorders are insufficient, inequitably distributed, and inefficiently used (5), especially in less developed countries (6). Most countries allocate less than 2% of their health budgets to mental health (7). This difference between health need (13%) and resource allocation (2%) has become known as the "treatment gap" (8).

One approach to reducing the treatment gap is through global policy. The World Federation for Mental Health (WFMH), in strategic alliance with the Movement for Global Mental Health, formed the "Great Push for Mental Health". A goal of this campaign is to ascertain what people with a personal or professional interest in mental health identify as priorities for services. From June to November 2012, we surveyed 473 WFMH members (comprising organizations and individuals) to establish priorities for mental health services of key civil society stakeholders, specifically including consumers, family members and professionals. The survey comprised general and specific priorities, characteristics of good community mental health care, and progress indicators informed by the Lancet Global Mental Health Group (9). Items were individually rated for importance, and four top priorities within each group were ranked. Organizations were grouped into low, middle or high income band using the World Bank Atlas method.

Responses were received from 96 organizations (20%), representing 15 low income (16%), 28 middle income (29%), 43 high income (45%) and 10 multiple (10%) countries. Fifty-nine (62%) represented service users (range 3 to 250,000, total 589,900), 49 (51%) represented family members (range 1 to 400,000, total 530,916), 50 (52%) represented mental health professionals (range 2 to 25,000, total 55,411) and 23 (24%) represented groups of mental health organizations (range 1 to 283, total 519). Sixty (63%) provided mental health services to a total of 681,761 (range 10 to 350,000) people, and 92 (96%) aimed to influence national mental health policy.

Respondents represented 53 countries: Afghanistan (n=2), Albania (n=2), Argentina, Australia (n=4), Austria (n=3), Bangladesh, Bosnia/Herzegovina, Brazil (n=2), Burundi, Cambodia, Canada (n=3), Cape Verde, China, Cook Islands, Democratic Republic of Congo, England/UK (n=2), Ethiopia, Fiji, France, Ghana (n=2), Gibraltar, Greece (n=4), Haiti, Hong Kong, Hungary, India (n=4), Ireland, Italy, Ivory Coast, Kenya (n=4), Lebanon, Luxembourg, Madagascar, Malawi, Malaysia (n=2), Malta (n=2), Mexico (n=3), Nepal (n=6), Netherlands, New Zealand (n=2), Nigeria (n=2), Peru, Portugal (n=2), Rwanda (n=2), Slovenia, Somaliland, South Africa (n=3), Spain, South Sudan, Swaziland, Tanzania, Uruguay and USA (n=12).

Logistic regression of income group on response showed that the 17% response rate from the 257 high income organizations was significantly ($\beta=.583$, $p<0.001$) lower than from the 38 low income (39%) and the 16 international (63%) organizations, but not from the 162 middle income (17%) organizations.

All eleven general priorities achieved consensus, demonstrating global agreement on the general principles for mental health systems. Highest ranked general priorities were "a national mental health policy or strategy" (no. 1), "promoting campaigns to eliminate stigma and discrimination" (no. 2), "strengthening and enabling psychosocial treatments aimed at recovery and where appropriate, return to work" (no. 3) and "facilitating the move from mental hospital to community care" (no. 4).

Fourteen out of the 18 specific priorities achieved consensus across income bands. Four (HIV/AIDS, man-made disasters including war, genocide and battle stress, natural disasters and tropical diseases) were rated highest in low income countries and lowest in high income countries. All income groups agreed that the highest priority is "enabling community-based treatment for mental illness".

All eleven characteristics of good community mental health care achieved consensus, indicating global consensus on the meaning of community care. The highest ranking characteristic was "there will be an effective programme for encouraging advocacy and research in the prevention of mental illness and disability and in the promotion of mental health".

All but two (proportion of involuntary admissions and proportion of psychiatrists) progress indicators achieved consensus. Highest ranked indicators were "specified budget for mental health as a proportion of total health budget" (no. 1); "presence of official policy, programmes, or plans for mental health, either including or accompanied by a policy on child and adolescent mental health" (no. 2), and "proportion of total mental health expenditure spent on community-based services, including primary and general health-care services" (no. 3).

Respondents were asked to specify a reasonable percentage of health budget to spend on mental health services. Although the response was continuous (i.e., not prespecified bands), there was consensus across all income groups that 10% of health budget should be allocated for mental health. Electronic technologies, person-centred care and consumer group involvement in policy-making were also all positively supported.

Finally, professional groups were rated for value for money. No income group differences were found, and rankings were psychiatric/mental health nurses (best value for money), followed in order by psychiatrists, general medical practitioners, social workers, community health workers, psychologists, support group members and general/physical health nurses (worst value for money).

To summarize, in this 53-country survey we demonstrated the emergence at the international level of cross-sectoral agreement on the appropriate structure for mental health services, including a greater orientation towards community rather than hospital care, with psychosocial and pharmacological treatments available from an adequately skilled workforce at primary and secondary care.

The highest identified priority was a national mental health strategy. Currently, there are marked differences across regions. Of the fifteen countries in East and South East Asia, fourteen (93%) have policy and ten (67%) have legislation (10). Across 53 European countries, 44 (83%) have policy and 50 (95%) have legislation (11), and across 34 Latin America countries, 24 (70%) have policy and three (10%) have legislation (12).

Community-based treatment was universally endorsed, but experience in China illustrates that translating pro-community mental health policy into reduced spend on hospitals remains difficult (13). Challenges identified across Africa include competing priorities, waning community engagement, and the non-sustainability of reliance on community volunteers (14).

The importance of person-centred care and consumer input to policy was highlighted. In English-speaking high income countries, this reflects a growing re-orientation of services towards recovery (15). A systematic review identified key recovery processes as connectedness, hope and optimism about the future, identity, meaning in life, and empowerment (giving the acronym CHIME) (16), although data were mainly from English-speaking countries (17). Understanding the meaning of recovery in other cultures is a research priority (18).

There is global consensus that a target of 10% of health spend should be allocated to mental health services. Redistributing resources to be more consistent with disease burden would allow "scaling up" of the coverage of services for mental disorders. Scaling up has emerged as an international priority (9), especially within low and middle income countries (19). The financial resource needed are modest: US$2 per person in low income countries, and US$3-4 in lower middle-income countries (20).

These results were conveyed to the World Health Organization for consideration and have been incorporated in the People's Charter for Mental Health.

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Are antidepressants clinically useful? Conclusion of a decade of debate

During the last decade, a number of meta-analyses have questioned the clinical usefulness of antidepressants, and exposed a significant publication bias and low effect size in comparison to placebo (1-9). The most important implication has been that antidepressants might not have any effect at all in mildly depressed patients (1,4,5). Several authors and agencies, such as the National Institute for Health and Clinical Excellence (NICE), have suggested the utilization of "alternative" treatment options (e.g., exercise and psychotherapy) in mildly depressed patients, and pharmacotherapy only for the most severe cases. An immediate consequence of this is that patients suffering from mild depression may be deprived from receiving antidepressants.

The Kirsch hypothesis concerning depression (10,11) is that there is a response which lies on a continuum from no intervention at all (e.g., waiting lists) to neutral placebo, then to active and augmented placebo including psychotherapy, and finally to antidepressants, which exert a slightly higher efficacy probably because blinding is imperfect due to side effects (enhanced placebo). This hypothesis has triggered much interest from the mass media and from intellects outside the mental health area, often with a biased and ideologically loaded approach (12).

Several authors have criticized the above hypothesis by focusing on the limitations of randomized controlled trials, on some limitations of Hamilton Depression Rating Scale (HDRS), and on the fact that the effectiveness of antidepressants in clinical practice is usually optimized by sequential and combined therapy approaches (13,14).

Two early efforts to re-analyze the Kirsch data set using different methodological approaches (15,16) independently reported results quite similar between them but different from those published by Kirsch. A recent multi-meta-analysis (17) utilized the Kirsch et al dataset and concluded that the most probable effect size of antidepressants relative to placebo is 0.34 (0.27-0.42) and that there is no significant effect of the initial severity of depression. The most probable raw HDRS score change after treatment with antidepressants is 2.82 (2.21-3.44). The same analysis showed that antidepressants are not equally effective, with venlafaxine being more effective than the rest and fluoxetine being the least effective.

The argument that a standardized mean difference (SMD) of 0.30-0.35 versus placebo is a weak one, suggesting that the treatment is not really working or does not make any clinically relevant difference, neglects the fact that such an effect size is the rule rather than the exception for efficacious treatments in psychiatry and medicine (e.g., 18). For comparison, one should look at the meta-analyses of the efficacy of medications for acute mania, reporting an SMD of 0.22-0.48 (19,20) while mania is clinically one of the easiest-to-treat acute psychiatric conditions.

The series of meta-analyses performed during the last decade made antidepressants perhaps the best meta-analytically studied class of drugs in the whole of medicine. The results of the recent multi-meta-analysis is likely to close the debate, suggesting that antidepressants are clearly superior to placebo and that their efficacy is unrelated to the initial severity of depression. Thus, there seems to be no scientific ground not to use antidepressants in mildly depressed patients.

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When psychiatrists are forced to deal with religion in daily practice

The Forum on religion and mental illness published in the February 2013 issue of *World Psychiatry* is a useful one. It reminds us of the necessity for psychiatrists to assess the religious/spiritual life of their patients and sometimes to include religious references in the case management of mental illness (1-4).

In many developed countries, it is easier to ask questions about the intimate sexual life of patients than questions about their religious/spiritual one. This reluctance to address religion and spirituality usually originates from patients themselves. On the contrary, in many low and middle income countries (LAMIC), religion is imposed as a necessary component by most patients and families and the reluctance comes from psychiatrists. The context is usually that of a traditional society (mostly rural and patriarchal, closeness to mother nature, vivid ancient beliefs…), progressively transforming itself into a modern way of life in cities. In these cases, the psychiatrist is often forced to deal with the religious beliefs of the patient and the family one way or another, despite his/her reluctance.

A good example of that is the belief in "jinn" in Islamic countries. The vast majority of Muslim communities considered some decades ago, and many still do, that epilepsy and some acute manifestations of mental illness are secondary to possession by spirits called "jinn". The concept of "jinn" is clearly mentioned in the Koran, the holy book of Muslims. Therefore, for many people in these countries, not to believe in these entities and their possessive action would be to shed doubt on the word of God. The traditional treatment proposed to patients suffering from epilepsy and other perceived possession states would be then to read the Koran, to visit tombs of saints, and to refrain from taking medication.

Some two decades ago, a patient suffering from epilepsy was asked in a saint's tomb near Marrakech, Morocco to stop her medication. She was severely burned when she fell into a fire during a fit and almost died when she fell into a small river nearby during another fit. The psychiatrist had to explain that she had an organic disease of the brain that absolutely necessitated an antiepileptic treatment. The psychiatrist did not forbid visits to saints' tombs or wearing talismans, but asked her not to stop the medication. Another patient having a schizoaffective disorder was exorcised by a traditional healer who asked him to stop his medications and gave him a "certificate of exorcism". The consequence was another psychotic episode during which the patient destroyed furniture in his workplace, for which the patient was condemned to 3 months in jail.

The question of "jinn" is often put forward by patients or families as an explanation for many mental disorder manifestations (hallucinations, neurotic fits, nightmares, manic episodes). These patients and families sometimes directly ask psychiatrists about whether they have the same religious frame of reference. The question is also asked by journalists when talking about mental disorders.

Having had to deal with such situations many times, I decided to address this issue in a more modern way. Instead of keeping the magical, supernatural, mythological approach of the "jinn" as the dominant explanation during the psychiatric interview, I suggested another interpretation to the patients: "According to Koran, 'jinn' are living beings, invisible; they can be good or bad, and they may be harmful if they enter the body (which is a kind of possession). This can be compared to microbes, bacteria and viruses". An episode of the life of the prophet Mohamed is also given to the patients and their families which reinforces this theory. The reaction to this proposed explanation of the mysterious force, the "jinn", was first surprise, then acceptance, and we then started talking about other aspects of the illness: symptoms, diagnosis, family and social aspects of the illness, treatment.

It is crystal clear that such an explanation will not be accepted by everybody and that some would completely refuse this modern way of looking at an ancient concept, a concept which was in existence long before the arrival of Islam. But we have about one billion and a half Muslims on this planet who believe in such entities because they are part of the holy book, and many would put them forward to explain a somatic or a psychiatric illness. Not to address this issue one way or another may hamper the doctor-patient relationship. For example, a patient who is convinced that his hallucinations come from jinn possessing him might hear less voices or no voice at all after a few weeks of treatment with an antipsychotic. The psychiatrist's comment might be "If you don't hear 'jinn' anymore, this might mean that they are sensitive to the action of medication; what do you think?".

It is useful to remind ourselves that 80% of the total population of the world live in LAMIC for whom religious/spiritual beliefs are an essential part of the everyday life of very many patients. The reluctance to address religion and spirituality will grow in LAMIC in the future, but for the time being, psychiatrists in these countries must keep them in mind when helping their patients.

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News from WPA Scientific Sections

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WPA Scientific Sections (current number is 68) continue playing an active part in the promotion and dissemination of scientific knowledge in different domains of psychiatry. Their work practically covers almost all aspects of our profession – from theory to practice, from clinical work to academic excellence, and from developing educational guidelines to service provision directions.

Sections enjoy a degree of independence within the framework of the WPA Statutes and By-Laws and it is heartening to note that, over the last many years, they have achieved an important position in WPA work. Their leaders are world renowned experts in their respective areas of expertise and have contributed to the promotion of psychiatry across many disciplines in mental health and allied fields.

According to the WPA By-Laws, Sections are required to highlight the current progress, analyse and disseminate information concerning their areas of know-how in research, education, teaching and training, and build ideas and suggestions for service provision. It is worth noting that the Sections have achieved these objectives by undertaking a number of activities, including organization of scientific meetings and symposia on topics of specialized interest to the professionals; organization of educational activities at different WPA meetings; development of educational programmes, guidelines, publications and proposals for adoption as WPA consensus and position statements, and conduction of international collaborative research.

During the current triennium, 36 WPA co-sponsored meetings have been organized by different Sections. Sections' presence has witnessed a prominence at WPA sponsored and co-sponsored meetings, with a total of 60 sessions. Moreover, organization of intersectional forums is the new addition to promote collaboration among Sections' work. Topics of education and suicide were chosen for these forums, that have been held at WPA conferences in Bucharest (Romania) and Vienna (Austria) during 2013. In addition to this, Sections have organized 19 educational programmes and courses, produced 9 guidelines, and published 28 books or monographs.

Sections' functioning is supervised by the Secretary for Sections and the Executive Committee and also supported by an Operational Committee, which includes experienced members of WPA offering valuable assistance (C.R. Soldatos, M. Amering, S. Harvey and T.E. Schlaepfer). At an organizational level, Sections regularly have their business meetings and hold elections every three years to elect their office bearers. Inclusion of new members to their list is also very encouraging and almost all Sections are getting interest from young psychiatrists.

The WPA has been improving its organizational image and identity in line with its Action Plans of 2008-2011 and 2011-2014. The official website of the WPA, along with its other media channels (WPA News, the official WPA newsletter, and the WPA E-Bulletin) has played an important role in this process. WPA Sections are very well represented on the website (1) and those other channels.

Several WPA Section experts are involved in the development of the ICD-11 and the relevant field trials. The work contributing to the process of harmonization between the ICD-11 and the DSM-5 is also assisted by many experts who are active members of various WPA sections (2-6). WPA Section members also continue contributing to *World Psychiatry*, the official journal of WPA, on different topics of current interest (7-13).

Future directions for Sections work include clustering of Sections on the basis of common interests and activities. It is hoped that the current enthusiasm in Section work will also lead further inputs to the excellence of scientific knowledge and innovations in psychiatric care practices for our patients. This certainly requires specialized expertise and it is anticipated that the current leadership of the Sections will be able to offer valuable guidance to the profession.

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Proposals for ICD-11: a report for WPA membership

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The production of the chapter on mental and behavioural disorders of the 11th edition of the International Classification of Diseases (ICD-11) is actively ongoing. The approval of the entire classification by the World Health Assembly is now expected in May 2017.

There will be at least two versions of the chapter: one for use in specialty settings (Clinical Descriptions and Diagnostic Guidelines) and one for use in primary care. Whether a specific version for research purposes will also be produced is still being discussed.

An important new development is that sleep-wake disorders and sexuality-related conditions and dysfunctions will be covered in separate chapters of the classification.

In the ICD-10, "non-organic" sleep disorders are included in the chapter on mental and behavioural disorders, while most "organic" sleep disorders appear in the chapter on diseases of the nervous system. This distinction has been regarded as obsolete. The new ICD-11 chapter on sleep-wake disorders will acknowledge that sleep disorders are a distinct area of practice requiring independent clinical attention.

Similarly, "non-organic" sexual dysfunctions are included in the ICD-10 chapter on mental and behavioural disorders, while most "organic" sexual dysfunctions appear in the chapter on diseases of the genitourinary system. The new ICD-11 chapter on sexuality-related conditions and dysfunctions will more appropriately reflect current clinical practice, acknowledging that sexual dysfunctions have both psychological and biological components.

The development of the ICD-11 chapter on mental disorders is being guided by an International Advisory Group, which is being supported by eleven working groups, dealing respectively with primary care, child and adolescent disorders, intellectual developmental disorders, personality disorders, psychotic disorders, somatic distress and dissociative disorders, stress-related disorders, substance-related and addictive disorders, mood and anxiety disorders, obsessive-compulsive and related disorders, feeding and eating disorders. Furthermore, there is a consultation group on older adults; two working groups, on neurocognitive disorders and on sleep disorders, report to the Advisory Groups for both Mental and Behavioural Disorders and Diseases of the Nervous System; and a working group on sexual disorders and sexual health reports to the Advisory Groups for both Mental and Behavioural Disorders and Reproductive Health.

The ICD-11 chapter on mental disorders is being produced in consultation with relevant stakeholders, including World Health Organization's member countries, several professional groups, and users of mental health services and their families. Attention to the cultural framework is being a key element. The revision is being seen as an opportunity to improve the classification's clinical utility, particularly in low- and middle-income countries (1-3).

The chapter will remain based on definitions and diagnostic guidelines for the various mental disorders, rather than on operational diagnostic criteria as in the DSM. The advantages and possible limitations of the two approaches have been recently discussed (4-10). A major argument in favour of the former approach is that it is congruent with the spontaneous clinical process, which does not involve checking in a given patient whether each of a series of symptoms is present or not, but rather checking whether the characteristics of the patient match the templates of mental disorders that the clinician has built in his/her mind.

A major effort has been made to harmonize the groups of disorders ("blocks") proposed for the ICD-11 with those included in the DSM-5. There will be, however, several differences at the level of specific diagnostic categories. Although final decisions concerning the contents of the ICD-11 have not been taken as yet, several expected convergences and divergences between the ICD-11 and the DSM-5 have been already discussed in the literature.

In the area of psychotic disorders, in the ICD-11 as in the DSM-5, Schneider's first-rank symptoms are going to be deemphasized in the description of schizophrenia, and the subtypes of that disorder are going to be omitted. Contrary to the DSM-5, the ICD-11 is expected to keep the one month duration criterion for the diagnosis of schizophrenia, and not to include functional impairment as a mandatory criterion (11,12).

In the area of mood disorders, in the ICD-11 as in the DSM-5, activation/increased energy is expected to be included as a defining symptom for mania, and it will be acknowledged that a manic/hypomanic syndrome emerging during antidepressant treatment, and persisting beyond the physiological effect of that treatment, qualifies for the diagnosis of manic/hypomanic episode. Furthermore, bipolar II disorder is going to be recognized as a distinct diagnostic entity in the ICD-11 (while it is just mentioned among "other bipolar affective disorders" in the ICD-10). Expected divergences between the ICD-11 and the DSM-5 will include a different characterization of mixed states and schizoaffective disorders. Moreover, the ICD-11 is going to exclude from the diagnosis of depressive episode, in line with the ICD-10 but differently from the DSM-5, "normal bereavement reactions appropriate to the culture of the individual concerned" (13-21).

In the ICD-11, acute stress reaction will be conceptualized as a normal reaction and thus classified in the section on "Factors influencing health status and encounters with health services", while "acute stress disorder" is

still included in the section on trauma- and stress-related disorders in the DSM-5. Furthermore, a new diagnostic category will be introduced in the ICD-11, named complex post-traumatic stress disorder (PTSD), marked by disturbance in the domains of affect, self-concept and relational functioning in addition to the three core features of PTSD (22).

In the area of eating disorders, the category of anorexia nervosa is expected to be broadened in the ICD-11 through dropping the requirement for amenorrhoea, extending the weight criterion to any significant underweight, and extending the cognitive criterion to include developmentally and culturally relevant presentations. Furthermore, a severity qualifier "with dangerously low body weight" is expected to distinguish the severe cases of anorexia nervosa that carry the riskiest prognosis. The bulimia nervosa category is likely to be extended to include subjective binge eating, and binge eating disorder is going to be included as a specific diagnostic category, in agreement with the DSM-5 (23).

Intellectual developmental disorders (a term replacing "mental retardation") will be defined as "a group of developmental conditions characterized by significant impairment of cognitive functions, which are associated with limitations of learning, adaptive behaviour and skills". Current subcategories based on clinical severity are going to be maintained, while problem behaviours will be described as associated features (24).

Preliminary reports from the working groups on somatic distress and dissociative disorders and on personality disorders are also available in the literature (25,26), and a more general discussion of diagnostic topics related to the ICD-11 and the DSM-5 can be found in recent issues of *World Psychiatry* and other journals (e.g., 21-41).

Two formative field studies have been undertaken early in the process of development of the ICD-11 chapter, in order to examine the views of mental health professionals around the world on the relationships among mental disorders, and to inform decisions about the structure of the classification (42,43).

Two global surveys of professionals' attitudes towards mental disorder classification have been carried out, one in collaboration with the WPA, involving nearly 5,000 psychiatrists in 44 countries (44), and one in collaboration with the International Union of Psychological Science, with the participation of 2,155 psychologists from 23 countries (45).

Field testing of proposals for the ICD-11 is being conducted using two approaches. The first is Internet-based field testing, which is being implemented through the Global Clinical Practice Network, a network of individual mental health and primary care practitioners currently including almost 10,000 registered participants from 127 countries. These Internet-based studies are using vignette methodologies to examine clinical decision-making in relationship to the proposed ICD-11 diagnostic categories and guidelines. The second approach is clinic-based field testing, which will assess the utility of proposed ICD-11 diagnostic guidelines in real-life clinical settings, with a special focus on low- and middle-income countries.

A series of symposia on the development of the ICD-11 chapter on mental disorders will take place within the World Congress of Psychiatry to be held in Madrid, Spain from 14 to 18 September 2014.

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