Time for a shift in focus in schizophrenia: from narrow phenotypes to broad endophenotypes

MARK WEISER, JIM VAN OS and MICHAEL DAVIDSON

Summary Many manifestations of mental illness, risk factors, course and even response to treatment are shared by several diagnostic groups. For example, cognitive and social impairments are present to some degree in most DSM and ICD diagnostic groups. The idea that diagnostic boundaries of mental illness, including schizophrenia, have to be redefined is reinforced by recent findings indicating that on the one hand multiple genetic factors, each exerting a small effect, come together to manifest as schizophrenia, and on the other hand, depending on interaction with the environment, the same genetic variations can present as diverse clinical phenotypes. Rather than attempting to find a unitary biological explanation for a DSM construct of schizophrenia, it would be reasonable to deconstruct it into the most basic manifestations, some of which are common with other DSM constructs, such as cognitive or social impairment, and then investigate the biological substrate of these manifestations.

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The recently announced National Institutes for Health (NIH) Neurosciences Blueprint (http://neuroscienceblueprint.nih.gov) defines the intention of the NIH to focus research efforts on three broad themes: development, degeneration and plasticity. This represents a major shift in research policy, by putting forward the notion that in order to facilitate progress in neuroscience, traditional approaches focusing on narrow phenotypes need to be brought together in a new collective effort focusing on much broader themes. Is a similar timely shift from the narrow to the broad applicable to schizophrenia research?

SHARED RISK FACTORS

Research over the past 15 years has elucidated a wealth of environmental and genetic effects and markers associated with increased risk for schizophrenia. However, because many of these putative effects and markers make the risk only 2–3 times greater, and given the relatively low prevalence of schizophrenia (0.5–1.0%), these findings have not enabled the identification of accurate markers or effects useful in predicting impending illness. The same research has also indicated that many of the risk factors identified are not specific to schizophrenia, but rather are shared with other psychiatric illnesses. For example, childhood adversity (Kessler *et al*, 1997), prenatal famine (Brown *et al*, 2000), migrant status (Fenta *et al*, 2004) and urban dwelling (Sundquist *et al*, 2004) are associated not only with later schizophrenia, but also with depression. Similarly, perinatal complications are associated not only with schizophrenia, but also with autism, anorexia nervosa and affective disorders (Verdoux, 2004). Stressful life events have been associated with the onset both of depression and of schizophrenia (Mazure, 1995).

Despite the non-specificity of risk, most of the associations are higher for schizophrenia than for other psychiatric diagnostic groups, with a gradient of severity between the magnitude of the association and the functional impairment attributed to the diagnosis. For example, in adolescents who meet criteria for non-psychotic disorders and are at increased risk of psychotic illness later in life (Weiser *et al*, 2001), the risk is higher in disorders with greater impact on social and vocational functioning, such as antisocial personality disorder and schizotypal personality disorder, and lower in disorders that cause the least social and vocational impairment, such as neurosis. If the phenomenology encompassed in the diagnosis of schizophrenia had a unique biological substrate, it would also be expected that the factors associated with increased risk would be uniquely linked to it. The non-specificity of the associations and the relationships between the strength of the association and the functional impairment is consistent with a multidimensional model along a continuum of severity.

Similar lack of specificity seems to be present when studying genetic and familial risk. For example, both brain-derived neurotrophic factor and catechol-O-methyltransferase (COMT) have been shown to be associated with schizophrenia (Egan *et al*, 2001) and also with affective disorders (Massat *et al*, 2004), and COMT is also associated with anxiety disorders (Arnold *et al*, 2004) and slight alterations in cognitive functioning (Egan *et al*, 2001). Studies of first-degree relatives of patients with schizophrenia have found them to be at increased risk not only of schizophrenia but also of affective disorders (Niemi *et al*, 2004). However, these 'shared' risk factors are not universal between all psychiatric disorders. For example, the risk of schizophrenia is increased in the relatives of patients with psychotic affective disorders, but not in the relatives of patients with non-psychotic affective disorders.

IMPAIRED COGNITIVE FUNCTIONING IN NON-PSYCHOTIC PSYCHIATRIC DISORDERS

The lack of specificity in relation to a continuum of impairment also appears when examining impaired cognitive functioning, a core feature of schizophrenia. We have recently shown (Weiser *et al*, 2004) that, in terms of mean effects across groups, adolescents suffering from psychiatric disorders have lower scores on cognitive tests compared with the general population, and that the more severe the decrease in functioning associated with the psychiatric disorder, the more severe the cognitive impairment associated with it. For example, whereas as a group adolescents with neurotic disorders had impaired cognitive scores of 0.4 standard deviation below the population mean, adolescents with personality disorders scored 0.6 s.d. below the mean, and adolescents with psychotic disorders scored 1.1

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s.d. below the population mean. Similar differences in cognitive impairment, measured decades before the onset of a psychiatric disorder, were apparent between people later diagnosed with schizophrenia or neurotic disorder in the UK 1946 birth cohort (van Os *et al*, 1999), a finding that has recently been replicated (David *et al*, 2005). Thus, cognitive impairment appears to be associated with the entire spectrum of psychiatric disorders, with schizophrenia representing the more severe end of this spectrum, exceeded only by learning disability (Weiser *et al*, 2004).

LACK OF DIAGNOSTIC SPECIFICITY

Lack of diagnostic specificity is also apparent in daily clinical practice. Whether manifestation of extreme anxiety in a socially maladjusted individual who several years earlier appeared to be psychotic represents comorbid anxiety in schizophrenia, or calls for a change of diagnosis, is a matter of diagnostic style rather than scientific rigour. Like psychiatric diagnoses, psychotropic medications also show broad overlap. Antipsychotic drugs have been shown to be effective in treating patients with affective and anxiety disorders, and some patients with schizophrenia benefit from treatment with antidepressants or anxiolytics. Practically, in some cases of chronic illness with a bad outcome, the phenotype of decreased functioning, neglect of personal hygiene, substance misuse, social isolation and cognitive impairment often makes it impossible to differentiate between patients with severe schizophrenia, post-traumatic stress disorder, obsessive–compulsive disorder, personality disorder, substance misuse or affective disorder.

The lack of specificity regarding risk factors, diagnoses and treatment may be related to our lack of understanding of the aetiology and pathophysiology of mental disorders. This situation may be analogous to the understanding of ischaemic heart disease several hundred years ago: then, before the aetiology and pathophysiology of the illness had been elucidated, there was probably no apparent connection between the crushing chest pain caused by occlusion of the left main coronary artery, inability to sleep flat caused by left heart failure, the swollen ankles caused by right heart failure, pain in the upper abdomen caused by stenosis of the right descending coronary artery and dementia caused by multiple small brain infarcts, all attributable to atherosclerosis. It was also not obvious how to distinguish between the transient elevation of blood glucose levels due to the stress of an acute myocardial infarction, which is an epiphenomenal marker of active illness not aetiologically related to the underlying atherosclerotic illness, and the abnormal values of blood glucose level due to diabetes mellitus, which is a marker of risk aetiologically related to the underlying illness. Moreover, it was not obvious several hundred years ago that different constellations of genes – such as genes predisposing to abnormal lipid metabolism, abnormal glucose metabolism and hypertension – can alone or in interaction increase the risk of the same atherosclerotic lesion. It is therefore feasible that when we understand the pathophysiology of mental illness, we will then be able to understand this overlap in risk factors, symptoms, diagnoses and treatment, or why the same patient, at different stages of the disease, may suffer from varying combinations of psychosis, affective symptoms and anxiety.

ENDOPHENOTYPES

Intermediate phenotypes, or endophenotypes, are measurable components along the pathophysiological pathway between aetiology and psychopathology. An endophenotype may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, neuropsychological or a personality trait, and represents simpler clues to the genetic and environmental underpinnings than the disease syndrome itself. Hence, in the probands and in their apparently healthy first-degree relatives it should be more prevalent than in the general population. Putative manifestations such as poor attention and other cognitive deficits (Niendam *et al*, 2003), decreased social drive (Laurent *et al*, 2000), stress sensitivity (Myin-Germeys *et al*, 2001) and a mood bias towards negative emotion (Maier *et al*, 1994) are present both in patients with schizophrenia and in their non-ill first-degree relatives more often than in the general population. However, given the overlap described above, it is likely that at least some of these endophenotypes may also be shared with other psychiatric disorders. This hypothesis is supported by the data on cognitive dysfunction in all psychiatric disorders mentioned above, and the non-specificity of other endophenotypes, such as stress sensitivity (Myin-Germeys *et al*, 2003) and negative mood bias (Hasler *et al*, 2004). Although there is much less research on aspects of social and emotional functioning in relatives of people with non-psychotic psychiatric disorders, there is evidence of premorbid social abnormalities in children who later develop anxiety disorders and depression (Caspi *et al*, 1996), and endophenotypes for depression are thought to include mood bias towards negative emotions, impaired learning and memory, neurovegetative signs, impaired executive cognitive function, psychomotor change and increased stress sensitivity (Hasler *et al*, 2004), all of which resemble reported endophenotypes for schizophrenia. Thus, analogous to the Neurosciences Blueprint initiative, we suggest that instead of focusing on discrete psychiatric entities, some relatively rare (like schizophrenia), and trying to attribute to them risk, markers and other effects, it might be productive to focus on a much broader spectrum of abnormal behaviours and emotions, and study phenomena shared by and associated with a broader array of diagnostic categories, such as impaired cognitive, social and emotional functioning. These endophenotypes are much more common than cases of schizophrenia, and may be markers of risk also for affective and anxiety disorders, which are much more common than schizophrenia. Thus, studying endophenotypes may be a realistic strategy to identify risk factors for mental illness. An additional advantage of focusing on studying these endophenotypes is that there are good animal models of cognition, emotion and social interactions, whereas the development of animal models for psychiatric illnesses has been problematic. Identifying risk factors might then further our understanding of pathophysiology, perhaps in a manner analogous to the understanding achieved when it was discovered that hypercholesterolaemia increases the risk of ischaemic heart disease, which then helped elucidate the function of cholesterol in the formation of the atherosclerotic plaque.

COMT AND COGNITION

An example of this that is closer to home may be taken from recent research indicating that the Met/Val substitution in the

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COMT gene may be associated with increased risk of schizophrenia (Egan *et al*, 2001). However, as mentioned, this substitution has also been found in patients with affective and anxiety disorders (Arnold *et al*, 2004; Massat *et al*, 2005). The underlying endophenotype in this case may be impaired cognition, as the Met/Val substitution in the COMT gene may be associated with slight alterations in aspects of cognitive functioning (Egan *et al*, 2001). Part of the pathway towards mental illness may therefore be the Met/Val substitution in COMT, which, by affecting cognitive functioning, may increase the risk of psychiatric illness in general, not only of schizophrenia.

CONCLUSIONS

Impaired cognitive, social and emotional functioning, which are endophenotypes of schizophrenia, may also be involved in the risk of other psychiatric disorders. Studying these endophenotypes might increase our understanding of risk of schizophrenia and of psychiatric morbidity as a whole. As psychiatric symptoms are present in almost half of the population, the implications of this research may be broader than studying risk of schizophrenia, which is much more rare.

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MARK WEISER, Department of Psychiatry, Sheba Medical Center, Tel-Hashomer and Sackler School of Medicine, Tel Aviv University, Ramat Aviv, Israel; JIM VAN OS, Department of Psychiatry and Neuropsychology, Maastricht University, The Netherlands and Division of Psychological Medicine, Institute of Psychiatry, UK; MICHAEL DAVIDSON, Department of Psychiatry, Sheba Medical Center, Tel-Hashomer and Sackler School of Medicine, Tel Aviv University, Ramat Aviv, Israel

Correspondence: Dr Mark Weiser, Psychiatric Outpatient Clinic, Sheba Medical Center, Ramat Gan, 52621, Israel. Tel: +972 52 666 6575; fax: +972 3 6358599; e-mail: mweiser@netvision.net.il

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