Does Schizophrenia Exist?

DS Goel*

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The question sounds rather strange, one hundred years after Kraepelin teased out *dementia praecox* (renamed *Schizophrenia* by Eugene Bleuler) and *manic depressive insanity*. Yet the title, borrowed from a recent Maudsley Discussion Paper [1], is more than mere rhetoric. As Kraepelin himself soon realised, the differentiation was a nosological artefact rather than a naturalistic entity, but it was hoped that once the specific neuropathological constellation underlying the disorder was found, the concept would become more concrete. More than a hundred years on, this has unfortunately not happened.

The International Pilot Study of Schizophrenia (IPSS), demonstrated the cross-cultural comparability of epidemiological data [2], as well as a remarkably stable clinical picture [3] and lifetime prevalence rates of around 1% of schizophrenia across national boundaries [4, 5]. These data, however, are an index of *reliability*, rather than *validity*. Irreverent critics [6] have compared this to *McDonald's* hamburgers, which taste the same regardless of where you buy them. The same holds good for the *Burger King* product which is as reliable. This leaves the crucial issue of *validity* open and the consumer has only the vendors' word that the product contains meat. Does it, really? Substitute *McDonald* with DSM and *Burger King* with ICD and the picture becomes clearer. The diagnosis of schizophrenia in both systems identifies individuals who are seriously unwell but who have little else in common. There is no evidence of a specific underlying brain disease [7]. Many patients have significant *mood* as well as *psychotic* symptoms [8], with the former often posing higher risk and requiring greater therapeutic effort [9]. Clinical features show a high degree of variability between individuals and within the same patient at different points of time [7]. The course and outcome of the disorder varies widely, and the consistently observed better prognosis, on five out of six course and outcome dimensions regardless of the

acuity of onset, in developing countries [3] has not been satisfactorily explained, though several contextual, primarily psychosocial factors have been proposed [10]. There is accumulating evidence for shared genetic/environmental risk factors and neurobiological abnormalities between schizophrenia and bipolar disorder [11]. Imaging studies have failed to reveal any consistent patterns of brain pathology and while a recent computational morphometry study flagged some grey matter changes specific to schizophrenia, this finding was undermined by white matter abnormalities common to both schizophrenia and bipolar disorder [12].

Evidence from Molecular Genetics

The most lethal blow to a unitary concept of schizophrenia comes from molecular genetics. Extensive genetic research has failed to identify any specific gene variance or combination specifically associated with schizophrenia [13,14]. Much of the evidence points to a significant overlap and commonality of genetic heritage between schizophrenia and bipolar disorder. Recent evidence from an appropriately designed twin study [15], suggests that certain genes confer susceptibility across the spectrum of schizoaffective disorder.

Reviewing the vast volume of literature on the subject, Jablensky [7] attempts to articulate a rational point of view which merits verbatim citation "The overview of evidence suggests that phenotypic variability has been confounding the search for the causes of schizophrenia since the inception of the diagnostic category. Attempts at redefining its boundaries by either 'lumping' or 'splitting' strategies have been undertaken over decades, with limited success. Most such attempts, based on various rearrangements of clinical symptoms and syndromes have ended in a failure to find natural boundaries between proposed clinical subtypes, either by locating a 'zone of rarity' between them, or by demonstrating a nonlinear relationship between the

* Consultant Psychiatrist, Southland Hospital Mental Health Services, Invercargill, New Zealand and formerly Senior Adviser (Psychiatry), Base Hospital Delhi Cantt.

symptom profiles and a validating variable. The inconsistent and poorly replicated results of genetic linkage and association studies using the diagnostic category as the sole schizophrenia phenotype are kindling discontent with the current nosology of schizophrenia, based on the recognition that ‘current nosology, now embedded in DSM-IV, although useful for other purposes, does not define phenotypes for genetic study. It is now almost certain that the current broad diagnostic concept of schizophrenia does not demarcate a specific genetic entity. Schizophrenia geneticists are facing a particularly difficult situation, seeking to discover specific genes contributing to an overinclusive diagnostic category for which no specific biological substrate has yet been identified – most likely due to extensive heterogeneity and an admixture of different underlying disease subtypes. It is doubtful that a specific genetic basis for a *causa prima* explaining the phenomenology of schizophrenia will ever be found. In contrast, it appears almost certain that the genetic polymorphisms and neurobiological deficits underlying schizophrenia are multiple, varied and partly shared with predisposition to other disorders, although they primarily express a ‘common final pathway’ within the schizophrenia spectrum. Such polymorphisms and deficits need not be intrinsically pathological and may represent extreme variants of normal structure and function. Above a certain density threshold, their additive or nonlinear interaction could give rise to the diagnostic symptoms in probands, but subclinical manifestations as endophenotype traits will be detectable in otherwise healthy people, with a higher relative risk in biological relatives of probands.”

Search for a way out

This climate of discontent has had several sequelae. At the level of clinical practice it has created confusion and a search for pragmatic alternatives. There is a general reluctance to diagnose schizophrenia except in the most severe cases and, in consequence, its use has declined more than 100% since the 1960s [16-18]. At another level, the concept of *schizophrenia spectrum disorders* has gained ground [19], based on the observation reported by Bleuler himself way back in 1920 and subsequently reinforced by the findings of the Danish-US adoptive study [20,21] that the genetic legacy of schizophrenia is shared with vulnerability to other related syndromes. The schizotypal disorder in ICD-10 [22] lies at the core of this concept.

However, the most intriguing and promising concept to emerge from the ongoing dialectic, this *atma-manthan* within psychiatry and medical genetics, has been that of the endophenotypes: measurable components between

and along the pathophysiological pathway between aetiology and psychopathology [23]. Though associated with the clinical disorder, these may not be part of the diagnostic criteria, are detectable before the onset of the active illness and have a genetic basis, being present amongst ‘normal’ family members with frequency higher than that for the general population [24]. The large number of candidate endophenotype markers identified and under investigation include cognitive (continuous performance tests, attention/vigilance based subtype, verbal dysmnestic subtype, verbal memory deficit-cortical/subcortical, dysexecutive type, prefrontal executive/working memory, frontal/abstraction deficit profile, spatial working memory), neurophysiological (electrodermal deviance, prepulse inhibition of startle response, deficient gating of auditory evoked response, P300 amplitude reduction/latency delay, N400 amplitude reduction, mismatch negativity, SPEM), neurological (soft signs, composite laterality phenotype, nailfold plexus visibility) and neuroimaging (fronto-thalamic grey matter deficit, fronto-stratal grey matter deficit, hypofrontality, MRI-derived 3 factor and whole brain nonlinear pattern phenotypes) [7]. It is conceivable that at some point in the not too distant future, the validation of some of these endophenotype markers may provide simple and inexpensive tests to facilitate early identification and targeted intervention in serious mental disorders [8].

Where do we go from here?

Where then do we stand today? *Does schizophrenia exist?* Probably not. At least not as a homogenous diagnostic monolith initially visualised by Kraepelin. I would like to compare the scenario to a child playing with building blocks, which can be fashioned into a house, church, or even a ship, depending upon the child’s ingenuity. The innovative concept of the endophenotypes offers exciting opportunities to refashion an ancient Greek term into a more dynamic *avatar*. This will have major implications for treatment and the *need to care* model proposed by Jim van Os offers significant advantages [25]. A major spin-off may be in the vexed realm of stigma reduction and render redundant calls for renaming schizophrenia, to which Japanese mental health professionals acquiesced in Aug 82, substituting it with *togo byo*, ‘integration disorder’ [26]. The time to jettison the concept finally is, however, still some distance away in the future and the situation was best summed up by McKenna while concluding his robust defence of schizophrenia “*as a good working hypothesis, useful until genuine aetiological groupings are discovered, at which time no one will be very surprised that it ultimately turned out to be more than one disorder.*” [27].

Epilogue

Finally, lest I be accused of attempting to upset the status quo and promote uncertainty, I would like to quote from the dialectic around the origins of the creation, recorded nearly four thousand years ago in the *Rigveda*, which reflects the spirit of unfettered scientific inquiry in its purest form:

“Who really knows? Who will there proclaim it? Whence it was produced? Whence this creation? The gods came afterwards, with the creation of the universe. Who then knows whence it has arisen?”

“Whence this creation has arisen – perhaps it formed itself, or perhaps it did not – the one who looks down on it, in the highest heaven, only he knows – or perhaps he does not know.”

Rigveda, 10. 129 [28]

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