The Nature of Schizophrenia: As Broad as it is Long

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The term schizophrenia has been used for many years both as a clinical diagnosis and to signify a disease entity for research into aetiology and pathogenesis. Generally, schizophrenia is defined in the same way in both settings, but here we will consider the suitability of the current schizophrenia construct for these two uses separately.

1. Schizophrenia as a diagnostic and syndromic construct

Current diagnostic approaches to schizophrenia define a psychiatric syndrome at the centre of which is the combination of positive, negative and disorganised symptoms (Tandon et al., 2013). However, there is significant variation in individual symptoms, mode of onset, course, and outcome (Owen et al., 2016; van Os and Kapur, 2009). In addition, positive, negative and disorganised symptoms are frequently accompanied by other associated features such as cognitive impairment, affective symptoms and movement disorders. As a consequence, schizophrenia lacks clear diagnostic boundaries, and symptom dimensions overlap with those of other psychiatric disorders, including bipolar disorder and childhood neurodevelopmental disorders (Craddock and Owen, 2005, 2010). In view of schizophrenia's dimensionality and heterogeneity, the DSM5 Psychotic Disorders Workgroup recommended eight dimensional assessments of symptoms and related clinical phenomena (including mania, depression, impaired cognition and abnormal psychomotor behaviour) for inclusion in the main text (Barch et al., 2013). Unfortunately, these were relegated to section 3 as requiring more study based on concerns that they may complicate clinical practice. Schizophrenia was also retained as a diagnostic construct in the ICD-11, but additional codes were added allowing clinicians to record dimensional information for positive, negative, depressive, manic, cognitive and psychomotor symptoms on three-point scales (Reed et al., 2019).

While we accept that there appears to be a consensus to retain schizophrenia as a diagnostic construct, it is our view that we should be doing everything we can to encourage and support clinicians to take a broader syndromic view of the condition than simply to assess the presence or not of the symptoms necessary to make a diagnosis (Figure 1). We need to ensure that clinicians capture the dimensional variety of symptoms and associated features and how they change over time. Developing and implementing reliable and clinically applicable

dimensional measures of these different domains, which clinicians are required to assess, should be a priority and will benefit clinical management as more individualised treatment selections can be made (Barch et al., 2013). Moreover, as the use of routinely collected electronic clinical data for research becomes increasingly feasible, it seems likely that the patients of the future will benefit if routine clinical assessment takes a broader and more nuanced view of the schizophrenia concept.

2. Schizophrenia as a disease construct

There has been much written about the shortcomings of current syndromic diagnoses in psychiatry as targets for aetiological and mechanistic research (Hyman, 2010; Owen, 2014) with some bold and imaginative solutions suggested (Insel et al., 2010). So, rather than re-tread old ground, we will consider what recent research has told us about the nature of schizophrenia as a disorder and try and refine it as a construct to guide future research. In particular we will consider three key issues: 1) is schizophrenia a disorder of particular brain regions or circuits, 2) when do the pathogenic events occur, and 3) why does schizophrenia happen?

2.1 Is schizophrenia a disorder of particular brain regions or circuits?

If we step back from the narrow group of symptoms and signs that are used to make a diagnosis, schizophrenia is revealed as a broad, pervasive, multi-domain disorder which impacts on most aspects of cognitive function (Green et al., 2019), and involves both motor (Perju-Dumbrava and Kempster, 2020) and sensory function (Javitt and Sweet, 2015). This is consistent with schizophrenia being associated with disturbances of many brain regions and circuits. This conclusion is now supported by recent large-scale structural imaging studies implicating reductions in brain size, cortical thickness and surface area as well as reduction in the size of many sub-cortical structures (van Erp et al., 2016; van Erp et al., 2018). Moreover, the largest GWAS of schizophrenia to date (PGC3) found that genes with high relative expression in most regions of the human brain were enriched for genetic variants associated with schizophrenia (Ripke et al., 2020).

PGC3 also showed an enrichment of common variant associations in genes expressed in CNS neurons, both excitatory and inhibitory, and to fundamental biological processes related to neuronal function (Ripke et al., 2020), including a number of gene sets related to synaptic structure and function in accord with findings from copy number variation (CNVs) and rare

coding variants (RCVs) (Fromer et al., 2014; Hall et al., 2015; Kirov et al., 2012; Pocklington et al., 2015; Singh et al., 2020).

Taken together, these findings suggest that underlying schizophrenia are fundamental disturbances of neuronal function that are not confined to a small number of brain structures (Figure 1). This would explain its diverse psychopathology, its association with a broad range of cognitive impairments, and the lack of regional specificity in neuroimaging measures associated with the disorder. These, and other (Hall et al., 2015), genomic findings offer robust starting points for mechanistic studies, experimental approaches, and model systems that need to be employed to understand fundamental disease mechanisms and to identify novel drug targets (Rees and Owen, 2020).

Of course, this is not to deny that particular symptoms, cognitive impairments or other features of schizophrenia are not associated with dysfunction in specific brain regions or circuits. Indeed, this is very likely to be the case. What it does mean however is that our questions in regard to relating brain and behaviour need to be framed carefully in the context of the phenotype in question and existing knowledge as to its underlying neurobiology (Insel et al., 2010). The implication of abnormalities of neuronal function in many brain regions, and the resulting pleiotropy, also means that researchers will need to be extremely careful in drawing causal inferences (O'Donovan and Owen, 2016).

2.2 When do the pathogenic events occur?

The idea that schizophrenia is a neurodevelopmental disorder is not new (Murray and Lewis, 1987; Weinberger, 1986). What has emerged more recently is the degree to which it shares aetiology and pathogenesis with congenital and childhood onset neurodevelopmental disorders (NDDs) such as intellectual disability, ASD and ADHD (Owen, 2014; Owen and O'Donovan, 2017; Owen et al., 2011). Many of the known environmental risk factors for schizophrenia impact on the developing brain and are shared with childhood NDDs (Owen et al., 2016). There is also overlap in risk loci between schizophrenia and childhood NDDs both within and between common and rare variants (Owen and O'Donovan, 2017; Rees et al., 2020; Ripke et al., 2020; Singh et al., 2020). Moreover, there is overlap with childhood NDDs at the level of specific risk alleles in schizophrenia, both CNVs and RCVs (Owen and O'Donovan, 2017; Rees et al., 2021). These findings support the view that schizophrenia is part of a continuum of neurodevelopmental disorders, perhaps reflecting a gradient of

underlying neurodevelopmental impairment (Owen, 2014; Owen and O'Donovan, 2017; Owen et al., 2011).

One might conclude that, if schizophrenia is essentially a neurodevelopmental disorder, this limits our hope of identifying therapeutically tractable mechanisms. However, there are several grounds for optimism. First, given the variability in outcomes of carriers of CNVs and RCVs, identifying the mechanisms which mitigate or modify sequelae might offer important opportunities for early intervention. Second, the synaptic, and other fundamental neuronal processes implicated by genomics, not only play important roles in neurodevelopment, but are also key to activities of the mature brain including cognition, learning and memory (Hall et al., 2015). These will likely be more tractable than early neurodevelopmental mechanisms. Third, as noted above, there is considerable variation in course and outcome of schizophrenia. Understanding the genetic and environmental factors that underlie this variation might offer new approaches to disease modification (Paternoster et al., 2017; Rees and Owen, 2020).

2.3 Why does schizophrenia happen?

Schizophrenia is polygenic and poly-environmental and in part at least reflects deleterious genetic variants and environmental exposures that impact on the developing brain (Keller, 2018; Owen et al., 2016; Pardinas et al., 2018; Rees et al., 2021). Building a human brain is one of the most complex tasks that nature has mastered and is not surprising that there are many things that can disrupt this process, and that the cumulative effects of such events can be pathogenic. This is not to say that outcomes are immutable, indeed as we have seen they are not. It is also likely that humans have evolved many mechanisms to mitigate the effects of adverse events on brain development and that these may be fruitful lines of therapeutic enquiry.

Not all environmental exposures associated with schizophrenia are obviously "neurodevelopmental" such as trauma, social adversities and cannabis use (Owen et al., 2016). The extent to which these associations are causal, rather than reflecting confounding, pleiotropy, or reverse causation remains to be fully established. As will be the question of whether, if they are casual, they impact on the same neurodevelopmental processes, whether there are important mechanisms at play that modify outcomes in the developmentally compromised brain, or whether there are forms of schizophrenia that are not neurodevelopmental.

3. Conclusions

Many lines of evidence point to the conclusion that what we call schizophrenia is a complex heterogeneous, multi-domain syndrome that can involve many functions and brain regions. There is considerable heterogeneity in symptom profile, course and outcome and in the presence of features that lie outside the core diagnostic criteria. Recent genomic data point to fundamental disturbances of neuronal and synaptic function that seem to affect multiple brain regions and functions. There is also strong evidence that supports and refines the neurodevelopmental hypothesis of schizophrenia by pointing to the existence of a neurodevelopmental continuum involving childhood NDDs and schizophrenia.

Clinically our patients will benefit from a broad syndromic constuct, which looks beyond making a categorical diagnosis based on the core features of positive, negative and disorganised symptoms, and that includes repeated dimensional assessment of key symptoms and clinical features over time, assessment of developmental history and comorbidities, and which recognises the fuzzy boundaries between diagnostic categories.

As researchers, we must face the complexity and heterogeneity of schizophrenia and the fact that, at higher levels of explanation seeking to relate brain dysfunction directly to behaviour, there is unlikely to be a single neurobiology of the disorder. Here we must deconstruct, or be doomed to fail.

Declaration of competing interest

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