

## Reappraisal

## Neurodevelopmental hypothesis of schizophrenia

Michael J. Owen, Michael C. O'Donovan, Anita Thapar and Nicholas Craddock

**Summary**

The neurodevelopmental hypothesis of schizophrenia provided a valuable framework that allowed a condition that usually presents with frank disorder in adolescence or early adulthood to be understood at least in part as a consequence of events occurring early in development. However, the implications of the neurodevelopmental hypothesis for nosological conceptions of the disorder can only now be fully appreciated. Recent research indicates genetic overlap between schizophrenia and syndromes in which psychopathology is manifest in childhood and that are often grouped together as 'neurodevelopmental disorders' such as autism-spectrum disorders, intellectual disability and attention-deficit hyperactivity disorder.

These findings challenge the aetiological basis of current diagnostic categories and, together with evidence for frequent comorbidity, suggest that we should view the functional psychoses as members of a group of related and overlapping syndromes that result in part from a combination of genetic and environmental effects on brain development and that are associated with specific and general impairments of cognitive function. This has important implications for future research and for the configuration of psychiatric services.

**Declaration of interest**

None.

It is now nearly a quarter of a century since Weinberger,<sup>1</sup> Murray & Lewis<sup>2</sup> formulated the neurodevelopmental hypothesis of schizophrenia. The idea that severe, adult mental illness has its origins in disturbed development of the nervous system had been proposed before,<sup>3</sup> but new impetus was given by several lines of evidence. Structural brain abnormalities were observed in neuroimaging studies and found to be present at the onset of illness yet there was an apparent absence of evidence for neurodegeneration in post-mortem studies. Second, the frequent occurrence at a young age of cognitive and motor abnormalities in those who subsequently develop frank illness was noted. Finally, the idea that adult-onset disorders could have their origins in development was supported by studies of primates that showed that neonatal lesions can have delayed effects on behaviour. The neurodevelopmental hypothesis has received much subsequent support from epidemiological, developmental and neuroimaging studies<sup>4</sup> and has been the dominant paradigm for schizophrenia research over the past two decades. Among other things it has led to an increasing focus on the importance of cognitive impairment in schizophrenia and the uncovering of widespread reductions in grey matter and ventricular enlargement by brain imaging studies.<sup>4</sup> However, it is our contention that the implications of the neurodevelopmental hypothesis of schizophrenia for nosological conceptions of the disorder, and thus for research into its aetiology and pathogenesis, can only now be fully appreciated. The predominant view of schizophrenia as a discrete disorder, or set of disorders, with specific causes, symptoms and consequences has been maintained by many factors.<sup>5</sup> In particular the evidence from family, twin and adoption studies has suggested that schizophrenia is not merely highly heritable, but that there exists a specificity of genetic risk with respect to other major psychiatric syndromes. However, recent findings pose severe challenges to this view, and suggest that schizophrenia might more usefully be seen as a member of a much wider group of overlapping syndromes to which neurodevelopmental abnormalities contribute, and which are not restricted to psychotic, or even psychiatric, disorders.

**Genetic risk**

Genetic epidemiology and population genetics suggest that a spectrum of allelic risk underlies complex traits like schizophrenia

and other common diseases.<sup>6,7</sup> There are contributions from alleles that are common in the population, but whose risk effects are small, as well as rare alleles, some of which have a large effect on disease risk. Empirical data now support the existence of risk alleles of both types in schizophrenia but suggest that neither class confers diagnostic specificity.

The lack of specificity of genetic risk for schizophrenia with regard to bipolar and other mood disorders has been suspected for some time.<sup>8</sup> In the last few years this has been confirmed by findings from genome-wide association studies<sup>9–11</sup> as well as adequately sized family studies.<sup>12</sup> These findings undermine the genetic support for schizophrenia as a discrete entity, and suggest that at least some of the genetic risk also influences risk for bipolar and other mood disorders. However, more surprising, and challenging for current nosological conceptions, have been recent findings that suggest genetic overlap between schizophrenia and syndromes in which psychopathology is manifest in childhood and that are often grouped together as 'neurodevelopmental disorders'.<sup>13</sup>

There is clear evidence for the involvement of several large, rare genomic copy number variants in schizophrenia, and it is likely that many more such variants will be implicated in the disorder over the coming years.<sup>10,14</sup> Copy number variants are submicroscopic deletions and duplications of segments of deoxyribonucleic acid that are important sources of individual genomic variation. Copy number variants can disrupt gene function by increasing or decreasing gene dosage, by perturbing normal regulation of expression, and possibly by as yet unknown mechanisms. One of the most intriguing and important findings to have emerged is that the specific copy number variants that are significantly associated with schizophrenia are also associated with a range of neurodevelopmental disorders such as autism-spectrum disorders, intellectual disability and attention-deficit hyperactivity disorder (ADHD) as well as other phenotypes such as generalised epilepsy.<sup>11,14</sup> It is important to note that there are no known schizophrenia-related copy number variants for which a severe psychiatric phenotype is inevitable, and, although they may occur *de novo*, they are also frequently transmitted from an apparently healthy parent. Moreover, when a phenotype is present, expressivity is highly variable, with phenotypes ranging from mild cognitive or physical anomalies through to schizophrenia,

intellectual disability, ADHD, epilepsy and autism even within the same family. These findings suggest that there may be a more general overlap in genetic risk and pathophysiology among these childhood disorders and between these disorders and schizophrenia, and challenge the view that these are completely unrelated diagnostic entities. There is a dearth of adequate family studies addressing these issues but some have shown increased rates of schizophrenia in the parents of individuals with autism<sup>15,16</sup> and intellectual disability<sup>17</sup> and of intellectual disability and ADHD in the relatives, particularly offspring, of probands with schizophrenia.<sup>17–19</sup>

### Comorbidity and overlapping syndromes

These findings remind us of the similarities in phenotype between schizophrenia and other neurodevelopmental syndromes. Importantly all are associated with impairments of cognition. They are all more common in males, and often associated with varying degrees of developmental delay, neurological soft signs and motor abnormalities. Moreover there is significant comorbidity between these syndromes that is often obscured by the use of diagnostic hierarchies or exclusions and by developmental change in predominant symptom type. Current service configurations also cause difficulties because of the administrative split between adult services and those treating children and adolescents, and between psychiatric, intellectual disability, and, in the case of epilepsy, general medical services. The reality is that there is substantial comorbidity between schizophrenia and intellectual disability<sup>20</sup> as well as between childhood-onset schizophrenia and autism/autism-spectrum disorders,<sup>21</sup> and symptoms of autism are also seen in adult schizophrenia.<sup>20,22</sup> Autism-spectrum disorder and ADHD also frequently co-occur<sup>23,24</sup> and rates of both are increased in those with intellectual disability.<sup>25</sup>

These findings challenge the view that these are completely unrelated diagnostic entities. Indeed, it is hard to avoid the conclusion that these disorders represent a continuum of genetic and environmentally induced neurodevelopmental impairment, rather than a set of aetiologically discrete entities, with the major clinical syndromes reflecting in part the severity and predominant pattern of abnormal brain development and resulting functional abnormalities as well as the modifying effects of other genetic and environmental factors. Thus autism is likely to be diagnosed when there are abnormalities of brain circuitry leading to prominent disorders of social communication; ADHD when abnormalities of inhibitory control are prominent; and intellectual disability when cognitive impairments are widespread. Over the past 10–15 years the importance of cognitive impairment in schizophrenia has been rediscovered and it is now clear that many individuals with a diagnosis of schizophrenia have a generalised cognitive impairment as well as a heterogeneous pattern of more specific impairments.<sup>26,27</sup> Cognitive impairments are also seen in bipolar disorder, but these are less severe and pervasive than in schizophrenia.<sup>28,29</sup> Interestingly, recent work suggests that copy number variants might play a less prominent role in the pathogenesis of bipolar disorder.<sup>30</sup> Under the assumption that large copy number variants are likely to have adverse consequences on brain development, these findings are consistent with the view that schizophrenia has a stronger neurodevelopmental component than bipolar disorder.

A simple conception of these findings is that severe mental illnesses occupy a gradient with the syndromes ordered by decreasing severity of neurodevelopmental impairment as follows; intellectual disability, autism, ADHD, schizophrenia, bipolar

disorder.<sup>9</sup> An elaboration of this view is that the key variables are the severity and extent of disruption of neural circuits with the extent (number and nature of neuronal circuits disrupted) determining the type of syndrome that results (intellectual disability, autism or schizophrenia etc.) and the severity (degree of disruption to individual circuits) determining the severity of the syndrome (severity of intellectual disability, severity of autism-spectrum disorder, severity of schizotypal disorder etc.). Of course it is likely that the precise nature and timing of critical events will also play a role as well as the modifying effects of genetic and environmental influences on factors such as the brain's capacity to buffer the effects of early damage, personality and propensity to affective disturbances.

### Implications

What is clear is that there is now an urgent need to re-examine and reappraise the relationships between these various syndromes. There has been much recent interest in the relationship between schizophrenia and bipolar disorder,<sup>5,9</sup> but there is now a need to focus upon the relationships among the neurodevelopmental syndromes that typically present in childhood and between these and the disorders that typically present in adulthood. There is a need for studies examining the clinical and familial overlap between these syndromes. Such studies would benefit from a focus on specific symptoms as well as cognitive and neurocognitive endophenotypes with the confounding effects of diagnostic practices removed. This needs to be coupled with more detailed analyses of the familial and molecular genetic relationships between each syndrome and the less severe manifestations that appear in relatives. Indeed, understanding the modifying and compensatory mechanisms that underlie variable expressivity and penetrance might point the way to new therapeutic opportunities. This work will need to take a developmental perspective since it is likely that the manifestations of these phenotypes will vary with age, and longitudinal studies will certainly be required. Aetiological research, including genetics, should now end its exclusive love affair with DSM and ICD categories. The goal now must be to relate research on aetiology and pathogenesis to specific psychopathological syndromes and phenotypes defined by studies of cognition and neuroimaging, and to place these in a developmental context.

Although recent genetic findings certainly challenge the aetiological basis of current diagnostic groupings, it would be premature to suggest a radical overhaul of diagnostic practices until more evidence accumulates. However, these findings do inform attempts as part of the DSM–5 and ICD–11 processes to create a meta-structure for psychiatric disorders based on aetiological and/or pathophysiological grounds.<sup>31</sup> They suggest that varying degrees of neurodevelopmental impairment might contribute across a broad spectrum of disorders with the final phenotype depending upon a complex dynamic of risk, protective, modifying and compensatory factors. These findings also have important implications for clinicians by suggesting that we should break down some of the service structures that currently serve to partition the management of individuals based upon current diagnostic categories. An obvious example is the separation between services treating general psychiatric disorders and intellectual disability.<sup>20</sup> The recent genetic data also add to evidence of continuities between childhood and adult psychiatric disorders<sup>13</sup> and suggest that greater communication and continuity between child and adult services is required.

In conclusion, the neurodevelopmental hypothesis of schizophrenia provided a valuable framework that allowed a

condition that usually presents with frank disorder in adolescence or early adulthood to be understood at least in part as a consequence of events occurring early in development. Recent findings suggest that we now need to go further and view the functional psychoses as members of a group of related and overlapping syndromes that result in part from a combination of genetic and environmental effects on brain development and that are associated with specific and general impairments of cognitive function.

**Michael J. Owen**, PhD FRCPsych, **Michael C. O'Donovan**, PhD FRCPsych, **Anita Thapar**, PhD FRCPsych, **Nicholas Craddock**, PhD FRCPsych, MRC Centre for Neuropsychiatric Genetics and Genomics and the Neuroscience and Mental Health Research Institute, Cardiff University, Cardiff, UK

**Correspondence:** Michael J. Owen, MRC Centre for Neuropsychiatric Genetics and Genomics, Henry Wellcome Building, School of Medicine, Cardiff University, Heath Park, Cardiff, CF14 4XN, UK. Email: owenmj@cardiff.ac.uk

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