

Editorial

Intellectual disability and major psychiatric disorders: a continuum of neurodevelopmental causality[†]

Michael J. Owen

**Summary**

There is accumulating evidence for shared genetic as well as environmental risk between intellectual disability and other conditions with a neurodevelopmental basis such as autism, attention-deficit hyperactivity disorder, epilepsy and schizophrenia. These can be conceived as lying along a

continuum of genetically and environmentally induced neurodevelopmental causality.

Declaration of interest

None.

Michael Owen is Director of the MRC Centre for Neuropsychiatric Genetics and Genomics and the Neuroscience and Mental Health Research Institute, Cardiff University.

The close relationship between severe psychiatric disorders and intellectual disability has been known for many years and certainly since Kraepelin laid the foundations for modern psychiatric classification. It is now well established that the prevalence of intellectual disability in schizophrenia is increased three- to five-fold, with the risk of schizophrenia in intellectual disability similarly increased.¹ There are several potential causes for this frequent comorbidity² but the evidence now favours the view that this reflects at least in part shared genetic aetiology.^{1,3} Cognitive impairment is an independent risk factor for schizophrenia as well as being a feature of the disorder; it is present in attenuated form in first-degree relatives, and evidence is accumulating for substantial familiarity across the two disorders.^{3,4} However, the most striking recent evidence for common genetic aetiology has come from molecular genetic studies showing that several large, rare genomic copy number variants (CNVs) substantially increase the risk of schizophrenia, and that these are also associated with intellectual disability and a range of other neurodevelopmental disorders such as autism-spectrum disorders, attention-deficit hyperactivity disorder (ADHD) and generalised epilepsy.³ These findings challenge the aetiological basis of current nosology and suggest that common mechanisms are operating across a range of disorders that tend to be researched and treated separately.

Familial risk

The epidemiological study by Morgan and colleagues⁴ in this issue adds to this burgeoning area of interest in two main ways. First, the findings suggest that there is a three-fold increased risk of intellectual disability in the offspring of mothers with bipolar disorder and major depression as well as those with schizophrenia. These findings are congruent with evidence for genetic overlap between schizophrenia and affective disorders and with suggestions that the three disorders lie on an aetiological and neurodevelopmental continuum.⁵ However, the evidence for an aetiological link between intellectual disability and affective

disorders is less strong than for schizophrenia and needs to be a focus for future studies.

One possibility arising from Morgan and colleagues' findings is that the increased rates of intellectual disability seen in the offspring of mothers with affective disorders reflect assortative mating. Indeed, 20% of affected children in the maternal schizophrenia group had a father with a psychiatric illness recorded on the psychiatric case register compared with 40% in the maternal bipolar group, 32% in the maternal unipolar group and 19% in the comparison group. However, the children of women with schizophrenia were more likely to have had no father registered at their birth than children in the other groups (21% compared with 9%, 5% and 4% respectively for maternal bipolar disorder, maternal unipolar disorder and the comparison children). It is also possible that environmental factors are playing a role in the outcomes seen in the offspring of the women with affective disorder. As the authors acknowledge, a significant weakness of the study is the absence of data on psychotropic medication. Although the risk of intellectual disability in offspring was not related to the timing of the onset of maternal psychiatric illness relative to the index birth for the children of mothers with schizophrenia or unipolar major depression, for children of mothers with bipolar disorder, the risk of intellectual disability was significantly increased only if onset of maternal illness predated the index birth. The authors are wisely cautious in drawing conclusions but note that this finding may reflect the role of medication taken during pregnancy and that mood stabilising drugs such as sodium valproate have been associated with an increased risk of congenital anomalies when used in pregnancy.

Obstetric complications

The second important finding of Morgan and colleagues is that obstetric complications, which have long been known to be associated with increased risk of intellectual disability, appear to act independently of familial risk.⁴ Obstetric complications have been consistently implicated as environmental risk factors for a range of neurodevelopmental disorders including non-syndromal intellectual disability, autism, ADHD, epilepsy and schizophrenia. The similarity between this range of outcomes and that seen in association with pathogenic CNVs is striking. In the 1950s Pasamanick and colleagues⁶ proposed the hypothesis of a 'continuum of reproductive causality' consisting of brain damage incurred during pregnancy or during or around birth leading to a

[†]See pp. 282–289, this issue.

gradient of injury extending from fetal and neonatal death through cerebral palsy, epilepsy, intellectual disability and behavioural disorder including schizophrenia. Given recent genetic findings it seems reasonable to modify this concept to encompass a continuum of genetically and environmentally induced neurodevelopmental causality along which lie intellectual disability, epilepsy, autism, ADHD and schizophrenia and possibly the major affective disorders.^{3,5} This view recognises the degree of aetiological and symptomatic overlap between diagnostic groups as well as the lack of clear diagnostic boundaries and sees 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.³

Implications

As Morgan and colleagues note, the mechanisms by which obstetric complications compromise neurodevelopment and confer risk for psychiatric and other disorders remain to be determined, and this is likely to prove challenging given the variety and complexity of the exposures involved.⁴ The nature of the relationship between obstetric and genetic risk factors is also uncertain, but it is parsimonious to assume that they confer risk by acting either additively or multiplicatively on common neurodevelopmental and neurobiological processes. The implication of specific genetic events, including not only CNVs but other classes of rare mutation, offers a means by which such processes can be identified and explored experimentally in animal and cellular models. For example, there is accumulating evidence that the genes disrupted by CNVs that confer risk for schizophrenia converge upon a small set of post-synaptic proteins that have been implicated in synaptic plasticity, which play key roles in neurodevelopment and cognition.⁷ It will be possible to study the effects of these mutations in experimental animals and also to model the impact of specific environmental exposures on relevant outcomes. It is also now possible to reprogramme somatic cells from humans into induced pluripotent stem cells and to derive neuronal cells from these stem cells.⁸ These and related techniques offer opportunities to create cellular models of individuals with specific disease phenotypes and to gain insights into developmental and other cellular and molecular phenotypes. Such models will likely have limitations but they offer the possibility of modelling disorders in which multiple genetic risk factors operate in individual cases and for creating platforms by which new therapeutic agents can be tested.

Finally, recent findings implicating shared aetiological factors across a range of disorders remind us how much we still have to learn from studying the interfaces and overlaps between current diagnostic categories. Much research still focuses on cases that

satisfy our current largely descriptive DSM and ICD categories and excludes those many 'comorbid' cases that do not neatly fit these. Current categories will remain useful for research so long as we expect heterogeneity and overlapping risk factors and mechanisms. However, we must also be prepared to explore novel dimensional and categorical approaches that cut across current categories and that might better capture underlying psychology and biology and to employ longitudinal and developmental designs. Mechanistic insights will also come from studies of endophenotypes.^{9,10} Here we will need a combination of top-down approaches, relating specific psychopathological syndromes to phenotypes defined by cognitive psychological and neuroscience rather than diagnosis, and bottom-up approaches relating genetics to fundamental measures of neuronal and synaptic function. These studies will increasingly be informed by close integration with observational and experimental studies of animal and cellular models.

Michael J. Owen, PhD, FRCPsych, MRC Centre for Neuropsychiatric Genetics and Genomics, and Neuroscience and Mental Health Research Institute, Cardiff University, Henry Wellcome Building, Heath Park, Cardiff CF14 4XN, UK. Email: owenmj@cardiff.ac.uk

First received 16 Dec 2011, accepted 20 Feb 2012

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