Attention-deficit hyperactivity disorder and the shifting sands of psychiatric nosology

Stephen V. Faraone

Summary

Larsson et al provide epidemiological evidence for a genetic association between attention-deficit hyperactivity disorder (ADHD) and both bipolar disorder and schizophrenia and Hamshere and colleagues confirm the latter association with genome-wide data. Although a genetic link between ADHD and bipolar disorder has been hypothesised for over a decade, the association with schizophrenia fills a notable gap in the literature. This editorial discusses the implications of these findings for clinicians, who must address psychiatric comorbidity in their treatment formulations, and researchers who are learning that the discrete categorical diagnoses of our diagnostic systems may not be up to the task of clarifying the causes and cures of psychopathology.

Declaration of interest

In the past year, S.V.F. received consulting income and/or research support from Shire, Akili Interactive Labs and Alcobra, and research support from the National Institutes of Health (NIH). His institution is seeking a patent for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received consulting fees or was on advisory boards or participated in continuing medical education programmes sponsored by: Shire, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. S.V.F. receives royalties for his books Straight Talk about Your Child’s Mental Health: What to Do When Something Seems Wrong (Guilford Press) and Schizophrenia: The Facts (Oxford University Press).

New data about comorbidity in ADHD

In this issue of the Journal, Larsson and colleagues continue this line of research. They present compelling evidence that ADHD shares genetic risk factors with both bipolar disorder and schizophrenia. A genetic association between schizophrenia and bipolar disorder has long been suspected and was recently confirmed with genome-wide association data. Hamshere et al now provide genome-wide association data suggesting that schizophrenia and ADHD share many common genetic variants. A genetic association between ADHD and bipolar disorder had been hypothesised over a decade ago and a familial link between the disorders was recently confirmed with meta-analysis. These data imply that ADHD should show a familial or genetic link to bipolar disorder, but these new data are the first to place that hypothesis on firm empirical ground.

Will these results influence clinical practice? I hope so. To begin with, the diagnosis of bipolar disorder among youth has been controversial, particularly among youth with ADHD. Family studies address such controversies because they can show associations between diagnoses at different developmental stages in the same family. Because the diagnosis of ADHD is not controversial in youth and the diagnosis of bipolar disorder is not controversial in adults, showing a familial link between ADHD in youth and parental bipolar disorder cannot be criticised for loose diagnoses of bipolar disorder in children. This trans-generational validation of the association between the two disorders thus strengthens the hypothesis that the two disorders co-occur in youth as they do in adults.

A recent meta-analysis provided insight into this issue. Among studies of adult relatives of patients with ADHD, the relative risk for bipolar disorder was 2.2. Among studies of child relatives, the relative risk for bipolar disorder was 2.1. These nearly comorbidity has biological roots; not only are many disorders comorbid in patients, they are also co-transmitted in families.

When Emil Kraepelin cleaved schizophrenia from bipolar disorder in the 19th century he set the course for a categorical, psychiatric nosology that would reign for more than a century. In the 1980s, the prevailing wisdom of the ICD and the American Psychiatric Association’s DSM, began the era of structured criteria with nosologies that operationalised Kraepeliane distinctions among disorders. Based on the DSM/ICD criteria of the 1980s, a hierarchical approach to diagnoses would exclude the diagnosis of some disorders if another disorder, which was higher on the hierarchy, could also be diagnosed. Patients with major depression could not be diagnosed with panic disorder; those with autism could not be diagnosed with attention-deficit hyperactivity disorder (ADHD). When faced with complex cases, the DSM/ICD paradigm tells clinicians to differentiate ‘primary’ from ‘secondary’ disorders.

Kraepelin’s approach has slowly crumbled under a weighty scientific literature. Today, patients with depression can be diagnosed with panic disorder and DSM-5 finally allows patients with autism to be diagnosed with ADHD. Signs of the DSM/ICD paradigm’s pathology are pervasive comorbidity, dimensionality and the existence of clinically important syndromes that do not correspond to diagnoses. Consider comorbidity. Starting with the Epidemiologic Catchment Area study of the 1980s, any epidemiological study assessing comorbidity has found that having one mental disorder puts patients at risk for having other mental disorders. This is true for children and adults, does not depend on methods of diagnosis and occurs in clinics and in the community. Family and twin studies find that

See pp. 103–106 and 107–111, this issue.
identical relative risks suggest that the familial link between ADHD and bipolar disorder cannot be accounted for by misdiagnosing youth with ADHD as having bipolar disorder. Such data help clinicians understand the validity of diagnosing bipolar disorder among youth with ADHD when the formulation of both diagnoses adheres strictly to diagnostic criteria.

Because ADHD comorbid with bipolar disorder is a highly disabling condition, missing the diagnosis of bipolar disorder in a child with ADHD will have deleterious consequences, which might have been avoided given the availability of treatments for bipolar disorder in children. Larsson et al’s findings suggest that clinicians be alert to the potential for relatives of patients with ADHD to have bipolar disorder. 1 Meta-analyses report the risk for bipolar disorder in families with ADHD to be 6.8% for offspring, 5.9% for siblings and 5.1% for parents. 2 This suggests that relatives of patients with ADHD be screened for bipolar disorder given that untreated bipolar disorder can lead to substantial adversity in the family environment.

The clinical implications of the genetic link between ADHD and schizophrenia are less clear given that the Larsson et al and Hamshere et al results are the first clear finding of such an association. Moreover, compared with bipolar disorder, schizophrenia is much rarer in youth and less likely to have an impact on clinical practice. But this finding does have clear implications for theory and research in psychiatry. From a theoretical perspective, these cross-disorder associations challenge the validity of the distinct Kraepelian categories instantiated by the DSM/ICD. The cross-disorder findings reported in this issue of the Journal are compelling, not only because of the high quality of the studies, but also because these studies are consistent with recent work in psychiatric genetics. There are many examples of widespread pleiotropic effects of risk variants on DSM/ICD categories, including statistically significant sharing of rare copy number variants for autism, ADHD and schizophrenia (e.g. Williams et al 3 ) as well as significant sharing of common variants implicated in genome-wide scans of schizophrenia, bipolar disorder, autism, depression and ADHD.4

Towards dimensional measures of psychopathology

Larsson et al’s data also provide a statistically powerful test of the hypothesis that ADHD plus bipolar disorder is a familial syndrome distinct from either ADHD or bipolar disorder when they occur alone. By finding an association between ADHD in the absence of bipolar disorder and bipolar disorder in the absence of ADHD, Larsson et al have refuted findings from several large family studies that found the two disorders to be co-transmitted within families (e.g. Biederman et al 5 ). Although more work is needed to clarify these discrepant results, the work of Larsson et al confirms a larger body of work suggesting that, in contrast to the DSM/ICD, it may be best to think of psychopathology in dimensional rather than categorical terms.

A good deal of data support the idea that psychopathology, and its underlying aetiology, are better described by dimensional rather than categorical constructs. In 1967, Gottesman & Shields 6 proposed a polygenic theory of schizophrenia that has since been confirmed with molecular genetic data showing not only that the aetiology of schizophrenia has a substantial polygenic component, but also that this polygenic aetiology overlaps with the aetiology of bipolar disorder. 7 The DSM/ICD paradigm deals with the dimensional nature of psychopathology by creating new categories that are mild versions of existing categories (e.g. schizophrenia and schizotypal personality disorder; major depression and dysthymia). If Larsson et al are correct, ADHD and bipolar disorder may fall on a genetic continuum of severity, with patients with ADHD but not bipolar disorder being at the mild end, patients with bipolar disorder but not ADHD having greater severity and patients with both ADHD and bipolar disorder having the greatest severity.

Other lines of evidence support the hypothesis that a dimensional perspective on ADHD is valid. Many studies have found an excellent correspondence between quantitative measures of ADHD and categorical diagnoses. These studies show that children with ADHD are at one extreme of a quantitative dimension and that, on this quantitative dimension, there is no obvious bimodality that separates children with ADHD from others. Moreover, people with symptoms of ADHD that do not exceed diagnostic thresholds show patterns of comorbidity, familial transmission and cortical thinning that suggest they have a mild form of ADHD. 8,9 Dimensional measures of ADHD are highly heritable, about 70–90%, which is similar to the heritability of the ADHD diagnosis (e.g. Sherman et al 10 ). And mathematical modelling of twin studies concludes that ADHD is best viewed as the extreme of a behaviour that varies throughout the entire population (e.g. Gjone et al 11 ).

Despite these considerations favouring a dimensional model of ADHD, the true underlying architecture of its aetiology may be more complex. Rare cases of ADHD are due to gross abnormalities of chromosomes. 12 We do not know whether the smaller deletions and duplications known as copy number variants also mark categorical cases. For most patients with ADHD, available data reject the idea that all these cases are caused by the exact same pattern of genetic mutations and adverse environmental exposures. Instead, there are likely to be several aetiological profiles of ADHD, which may correspond to varying degrees of compromise in the neural networks that underlie the disorder.

Unravelling such complexities leaves a difficult task for ADHD researchers. Although hi-tech developments in neuroscience and molecular genetics may be up to that task, Larsson et al’s work reminds us that the low-tech tools of genetic epidemiology still play a key role in our quest to understand the aetiology of ADHD and its links to other disorders.

References


King George III (1738–1820): re-evaluation of his mental health issues

Timothy Peters

The unqualified practitioner must not be let loose, not even on the dead
Sir Lewis Namier, Personalities and Powers (1955)

The mental health disorders of George III, their causes and consequences are important issues for historians. If accurate and correctly interpreted, they will provide valuable insights into his behaviour and decisions during his 50-year reign.

George was born 2 months premature and unlikely to survive. After a somewhat dysfunctional childhood and adolescence, he succeeded to the throne aged 22. Initially, his reign was turbulent, with frequent changes of ministers, and it was only in 1783 with the appointment of William Pitt as First Minister that he had a more stable government.

George had four, possibly five, episodes of mental ill health. In 1765 during this turbulent period, he had recurrent chest infections with some features suggestive of depression but no medical notes are extant. In 1788–1789 he had his first episode of serious mental ill health following probable cholelithiasis for which he spent 5 weeks taking the waters at Cheltenham. His behaviour during this period is suggestive of hypomania and was followed in October 1788 by an episode of acute mania meeting the DSM-IV and ICD-10 criteria. Recent studies using the OPCRIT programme support this diagnosis: the Young Mania Scale indicates a severe episode of mania (grade 4/4).

There are more than 100 volumes of medical notes together with many primary sources describing his behaviour during this and subsequent periods of mental ill health. By March 1789 he was in remission for 12 years before relapses in 1801, 1804 and 1810. During the intercurrent periods, there is evidence from his writings and behaviour of possible dysthymia and after his 1810 episode at the age of 70 he had a decade of chronic mental ill health, the subject of current research by my colleagues and I.

Variegate porphyria is one of the rarer forms of acute porphyria with a patient prevalence of 3 per million. Attacks are usually precipitated by exposure to medicinal agents unavailable to George III and characterised by severe abdominal pain often extending to the lower back and thighs. It is persistent, unrelenting and certainly not colicky or cramping, a feature of George’s episodes. There are characteristic photosensitive skin lesions also not seen in George. Psychiatric symptomatology, usually a transient confusional state, occurs in less than 1% of acute attacks. Untreated severe attacks are often fatal or recur with increasing frequency and severity. From the prevalence data it would be predicted that some 180 living descendants would have clinically manifest porphyria; none have been reported.

In 1964, Ida Macalpine and Richard Hunter, mother and son psychiatrists, categorically stated that George was not ‘psychiatrically ill’ but suffered from acute intermittent porphyria later changed to the rarer and milder variegate porphyria; they rejected three detailed papers by experienced American psychiatrists reporting manic-depressive psychosis. In spite of detailed objections by porphyria experts, Macalpine and Hunter were able to garner support from historians, some psychiatrists and, surprisingly, The Royal Society. With the support of the play and film The Madness of King George by the former historian Alan Bennett and the composition Eight Songs for a Mad King by Peter Maxwell Davies, the diagnosis has gained general acceptance.

It might be argued that their claims, now shown to be unfounded, are of little current concern. However, their diagnosis has had untoward consequences. The diagnosis of acute porphyria rather than bipolar disorder has inhibited historians from providing explanations of George’s final decade of cognitive impairment, his offers of abdication at times of stress, his persistence with policies well after their failure and the damaging relationships with his children. Finally, the portrayal of the incorrect diagnosis and by insinuation his apparent mistreatment has distorted the contributions of the King’s specialist ‘mad doctors’, Dr Francis Willis and his colleagues, to the development of effective psychiatric practice.
Attention-deficit hyperactivity disorder and the shifting sands of psychiatric nosology

Stephen V. Faraone

BJP 2013, 203:81-83.
Access the most recent version at DOI: 10.1192/bjp.bp.113.126524

References
This article cites 12 articles, 3 of which you can access for free at:
http://bjp.rcpsych.org/content/203/2/81#BIBL

Reprints/permissions
To obtain reprints or permission to reproduce material from this paper, please write to permissions@rcpsych.ac.uk

You can respond to this article at
/letters/submit/bjprcpsych;203/2/81

Downloaded from
http://bjp.rcpsych.org/ on June 26, 2017
Published by The Royal College of Psychiatrists

To subscribe to The British Journal of Psychiatry go to:
http://bjp.rcpsych.org/site/subscriptions/