I’m Andrew Amos, and this is the November 2013 issue of Australian Psychiatry Review. This month concludes with a focus section on psychiatric genetics, rejuvenated by recent replications of genome-wide association studies. Other highlights of the literature reviewed this month include Atigari and Healy’s suggestion that the proconvulsant effects of clozapine, lithium, and ketamine, may be a novel therapeutic principle rather than a side-effect. Jelovac and colleagues provide a systematic review showing maintenance ECT does not change relapse after a primary ECT course. Zipursky and colleagues persuasively argue against what they describe as the myth that schizophrenia is a neurodegenerative disorder. Finally, Priebe and colleagues report that small financial incentives can greatly increase treatment adherence in previously poorly adherent patients on depot antipsychotics.

ANZJP - November
In November the ANZJP includes a cognitive remediation trial by Tan and King, who randomised 70 Singaporean patients with schizophrenia to a 60-hour cognitive remediation program or physical exercise. Cognitive remediation comprised computer-assisted cognitive exercises for up to 5 hours per week over 12 weeks, and fortnightly cognitive-based counselling which continued monthly after the computer-assisted programme finished. Patients were paid a small amount for each hour of computer exercises or physical training they completed. They found significantly greater improvements for cognitive remediation patients on all neurocognitive measures, with better vocational and independent living skills and better functional outcomes at one year follow-up, including more wages from competitive employment; while the physical exercise patients showed better physical fitness.

Atigari and Healy draw attention to the proconvulsant mechanism of certain psychotropic treatments. Grounding their analysis in the initial division of psychotropics into the general therapeutic principles of sedation and stimulation in the 1950s, they trace the growing complexity of efforts to describe and understand classes of psychotropics based on structure, effects, and theoretical considerations. Atigari and Healy imply that the drive towards categorisation in late twentieth century psychiatric diagnosis with DSM-III was associated with the linkage of psychotropic medications to specific indications, ignoring evidence of more general mechanisms. An example is the creation of the idea of ‘mood stabilisers’ applied to anticonvulsants to provide a magic bullet for the target market of mania, replacing the poorly defined therapeutic principle of a general sedative action which could be applied to many states characterised by increased CNS activity. Atigari and Healy note clozapine’s unique efficacy, and the failure of attempts to reproduce its efficacy in the absence of putative side effects such as agranulocytosis and seizure diathesis. Adverting to the unique therapeutic effects associated with treatments including lithium, ketamine, and ECT, Atigari and Healy speculate that there may be a general pro-convulsant therapeutic principle analogous to the original sedative and stimulant principles.

In November, Malhi and Henderson debate Goldberg on the place of anxiety within psychiatry. With more than a faint echo of steps towards dimensional diagnosis in the DSM-5, Goldberg proposes the centrality of anxiety in mental disorders. He refers to evidence that anxiety is a general risk factor for psychiatric diagnoses, higher severity, and worse outcomes including suicide. Against this empirical approach Malhi and Henderson balance a structural model with unique anxiety factors, such as hyperarousal and tension, and unique depressive factors, such as anhedonia and absence of positive affect, as well as a higher-order factor called general distress comprising non-affective and affective symptoms. Noting the opposing deficiencies of treating anxiety as a diagnosis rather than as groups of symptoms, Malhi and Henderson question whether it is possible that anxiety and depression are a single entity with manifold presentations, quoting a ‘syndromal combined anxiety and depressive disorder’ called ‘cothymia’ by Tyrer. They agree with Goldberg that the DSM-5 does not adequately characterise anxiety, but differ on the important unresolved questions.
In October the American Journal of Psychiatry includes an article by Murrough and colleagues which asks whether ketamine is ready for clinical use. They describe a retrospective cohort study of the Tennessee Medicaid program with close to 30,000 recent initiators of antipsychotic medications and 15,000 controls, excluding patients with a previous diagnosis of diabetes or schizophrenia. They found that those prescribed antipsychotics had a 3-fold, dose dependent increased risk of type 2 diabetes in the first year of follow-up. The risk was greater in children 6 to 17 years old, and with atypical antipsychotics.

An editorial by Heckers evaluates the challenge by Kahn and Keefe to the received wisdom that schizophrenia is primarily a disorder of psychosis, to argue that the primary dysfunction in schizophrenia is one of cognition. Kahn and Keefe rely on the central place of cognitive deficits in the original descriptions of dementia praecox and schizophrenia by Kraepelin and Bleuler, the enduring presence of cognitive deficits well before and long after the onset of psychosis, and argue for a specificity of cognitive deficits in schizophrenia not seen, for example, in bipolar disorder. Kahn and Keefe propose that early intervention efforts that wait until the onset of psychotic symptoms such as hallucinations and delusions are too late, given evidence of cognitive decline decades earlier. Heckers acknowledges the many associations between cognitive and functional decline and subsets of patients with schizophrenia, but notes that cognitive deficits are not ubiquitous in schizophrenia, and psychosis is far from ubiquitous amongst those with cognitive deficits.

Furthermore, the evidence distinguishing cognitive outcomes in schizophrenia from those in bipolar or schizo-affective disorders is equivocal and in the process of revision. Heckers also faults Kahn and Keefe for failing to address the possibility of recovery from psychotic illness despite increasing evidence that this occurs in a substantial minority. Finally, the impractical nature of Kahn and Keefe’s proposal that the core component of schizophrenia be detected in the inability of young people to develop cognitively is demonstrated by their suggestion that this be facilitated by cognitive growth curves based on large longitudinal cognitive databases. Implicitly this acknowledges that we do not have the capacity to adequately characterise cognitive decline predictive of schizophrenia as opposed to other developmental disorders. Given these criticisms, Heckers is unwilling to accept Kahn and Keefe’s proposal that cognitive decline become a criterion for the diagnosis of schizophrenia.
as well as a central target of treatment.

Molecular Psychiatry - See focus section.

Biological Psychiatry - 1 November, 15 November

The 1st November edition of Biological Psychiatry includes many articles exploring the relationship between glucocorticoids, trauma, and brain development, with applications to PTSD. Steudte and colleagues showed that levels of cortisol in hair follicles but not in saliva may act as markers of trauma exposure, with increased trauma associated with sustained hypocortisolism. They conclude that hair follicle cortisol may be a more accurate measure of chronic stress hormones than previous measures. Using MRIs in healthy 6-10 year olds, Davis and colleagues showed that fetal exposure to synthetic glucocorticoids was associated with later cortical thinning, most prominently in the anterior cingulate cortex. Cortical thinning was associated with higher affective symptoms in these children.

Biological Psychiatry have published online a neuroimmunological perspective by Coutinho and colleagues which describes disturbances associated with autoantibodies targeting neuronal surface proteins and considers antibody mediated central nervous system disease. They note that the brain was originally considered immunologically privileged and not prone to autoimmune disease due to the blood brain barrier. Since 2001 multiple encephalopathic presentations have been linked with autoantibodies targeting central nervous system epitopes, including the NMDA receptor, the voltage gated potassium channel, the AMPA receptor, the GABAB receptor, and the glycine receptor. Coutinho and colleagues review evidence linking immune processes and psychosis, including increased autoimmunity in patients and relatives, inflammation-related gene involvement, and Deakin and colleagues’ paper demonstrating a small proportion of patients with clinically typical schizophrenia have autoantibodies against the NMDA receptor and other neuronal antigens.

The 15th November issue of Biological Psychiatry includes research and editorials on speculative new treatments for depression. Dinan and colleagues review evidence on psychobiotics, defined as live organisms which, when ingested, improve psychiatric symptoms. While the evidence remains suggestive rather than conclusive, the authors examine biotic interactions with inflammatory cascades, infection, the hypothalamo-pituitary-adrenal axis, and neurotransmitters. Huang and colleagues report evidence from animal and human studies of the antidepressant effects of the glycine transport inhibitor sarcosine. They found that sarcosine decreased analogs of depressive behaviour in murine models of depression, and substantially improved scores on the Hamilton Depression Rating Scale in a six week randomised citalopram controlled trial in Taiwanese patients with major depressive disorder. They speculate that the problematic antidepressant effects of both NMDA agonists and antagonists are resolved by differential effects at synaptic and extrasynaptic NMDA receptors. Voelli and colleagues describe common mechanisms linking the rapid antidepressant effects of ketamine and scopolamine. A related editorial by Monteggia and Kavalali proposes that the common mechanism of rapid antidepressant action may be increased glutamatergic synaptic efficacy.

Neuropsychopharmacology - November 2013

An article by Jelovac and colleagues in the November Neuropsychopharmacology provides a systematic review and meta-analyses of post-ECT relapse in responders with major depressive disorder. They found that 50% of patients relapsed within 12 months, with 37% relapsing in the first six months. Relapse rates in the first six months after ECT were similar in patients treated with and without maintenance ECT, while antidepressant relapse after ECT halved relapse rates versus placebo. The evidence base is most established for tricyclic antidepressants, with limited evidence regarding newer antidepressants or augmenting regimes.

Schizophrenia Bulletin - November 2013

In November Schizophrenia Bulletin includes a diverse set of articles. The issue opens with an editorial by Faroq and colleagues proposing the use of treatment response to subtype schizophrenia. They base their proposal on the inadequacies of current subtypes based on polythetic symptom clusters with specifiers of course and severity, and severe deficiencies in approaches based on biomarkers and clinical staging. They compare the use of clozapine in treatment resistant schizophrenia with insulin and non-insulin dependent diabetes, and suggest three levels of schizophrenia: antipsychotic responsive schizophrenia, clozapine responsive schizophrenia, and clozapine resistant schizophrenia.

Kirkpatrick and Miller give an overview of the relationship between inflammation and schizophrenia, concluding that while the evidence is provocative, the number of studies is small and progress requires improved methodological rigor and replication studies.

Selten and colleagues give an update on the social defeat hypothesis of schizophrenia, which suggests that the sustained exposure to the negative experience of exclusion from the majority group increases the risk of schizophrenia by sensitisation of the mesolimbic dopamine system. The literature links social defeat to 5 risk factors, with the strongest evidence for migration and childhood trauma, with insufficient evidence for urban upbringing, low intelligence, and drug abuse. Selten and colleagues note that evidence for sensitisation of the mesolimbic dopamine pathway remains preliminary, and explore criticisms, including that social defeat is a consequence of schizophrenia rather than a cause, and that social defeat is not a specific risk factor. Stilo and colleagues report an investigation of social disadvantage in schizophrenia which found an association between markers of childhood and adult disadvantage and schizophrenia. Separation from or death of a parent in childhood showed the strongest association with schizophrenia. Despite the post-hoc, cross-sectional nature of the study, Stilo and colleagues propose an aetiological role for social disadvantage in schizophrenia, and tentatively suggest that reducing social disadvantage may protect against it.

Barkhof and colleagues report a trial where 114 patients in Amsterdam who experienced a psychotic relapse in the context of treatment non-adherence in the previous year were randomly assigned to an adapted form of motivational interviewing for adherence, or an active control condition. While motivational interviewing did not improve adherence, it may reduce hospitalisation overall, motivational interviewing did reduce hospitalisation rates for females, non-cannabis users, younger patients, and patients with shorter illness duration, leading Barkhof and colleagues to suggest motivational interviewing for targeted groups of patients.

Johannesen and colleagues report an effort to establish event related potentials as endophenotypes for schizophrenia. Endophenotypes are phenotypes thought to mediate between genes and psychiatric symptoms, such as expression of the catechol-o-methyl-transferase protein thought to mediate between a gene and the negative symptoms of schizophrenia. Event related potentials are features of EEGs triggered by events such as somatosensory stimuli. Johannesen and colleagues establish that the ERPs P50, P300, and supplemental measures classified schizophrenia in patients from healthy controls with 70% specificity and sensitivity, but did not differentiate schizophrenia patients from bipolar patients. The authors speculate that this is consistent with models that suggest schizophrenia and bipolar disorder share significant underlying pathophysiology.

Based on evidence linking psychosis to immune system dysfunction, a meta-analysis of adjunctive NSAIDs added to antipsychotics for patients with schizophrenia by Nitta and colleagues found little evidence of improvement.

Freeman and colleagues examine how cognitive/affective biases may play a role in maintaining paranoid delusions, with paranoia associated with greater anticipation of threat events, negative interpretations of ambiguous events, a self-focused cognitive style, and negative ideas about the self. They conclude that treatment of emotional dysfunction should reduce psychotic experiences, including shifting attentional focus.

Jaaskelainen and colleagues report a meta-analysis that collected data from 50 studies on...
recovery in schizophrenia. They found that only 1 in 7 patients improved significantly on both clinical and social measures with improvements sustained for at least 2 years. With more rigorous methodology than previous meta-analyses they found lower rates of recovery, did not find different rates of recovery for men and women, and did not find evidence of increasing rates of recovery with recent efforts at early identification and treatment of longer follow-up.

Zipursky and colleagues argue against the myth that schizophrenia is a neurodegenerative illness. They suggest that while ¼ of patients with schizophrenia have a poor outcome, few show a progressive loss of function characteristic of neurodegeneration; MRI studies show neurodevelopmental abnormalities at first episode with ongoing volume decreases which are explicable as the effects of antipsychotic medication and substance abuse; and cognitive deficits compared to healthy controls which are present at the time of first episode psychosis but then do not deteriorate with time. They propose that individual cases of deteriorating function may be attributed to poor adherence to treatment, comorbid conditions, and social disadvantage. They conclude that most people with schizophrenia can achieve a substantial degree of recovery with appropriate treatment. Zipursky and colleagues explain clinician pessimism regarding outcomes of schizophrenia by reference to the “Clinician’s Illusion”, which suggests that doctors often attribute the characteristics and course of those currently ill to all those with an illness. As the patients being seen by psychiatrists are generally the most stably unwell, these characteristics are projected onto all people who have experienced psychotic illness, discounting the substantial proportion of people who recover some or all function.

Journal of Clinical Psychiatry - September 2013

In September the Journal of Clinical Psychiatry reported a 10 year Taiwanese registry study by Wu and colleagues that there is an increased rate of venous thromboembolism in the acute phase of treatment of refractory depression, with the use of deep brain stimulation for the treatment of refractory depression, with significant improvements. Underwood provides a journalistic review of the use of deep brain stimulation for the treatment of refractory depression, with around half of 200 patients showing significant improvements. The article proposes that DBS has allowed researchers to test the theory that depression is not a result of chemical imbalance, but rather of deranged brain circuits. Markov and colleagues challenge recent representations of human brains as small-world networks, reporting evidence of high-density cortical graphs that are better modelled as hierarchical networks with complex reciprocal links between a dense core and specialised periphery.

International Medical Journals
Science, Nature Reviews, Neuroscience, JAMA, Lancet, BMJ

Science

On 1st November the journal Science released a special neuroscience issue called “The Heavily Connected Brain” with articles outlining recent advances in understanding of the organising networks of the human brain. Park and Friston review network theoretical models that attempt to explain the relationships between brain structural features and functional outcomes such as cognitive processes. Turk-Browne reviews large-scale fMRI data analyses which examine functional connections between brain regions during cognitive tasks, with increasing computational power allowing the temporal correlation of millimetre scale subdivisions across the entire brain.

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Online Psychiatry Resources
- Selected video lectures

Brain and Behaviour Research Foundation
Collection of psychiatric lectures
http://bbrfoundation.org/meet-the-scientist-webinar-series#recordings

Massachusetts General Hospital CME
Collection of medical lectures
Includes large number of psychiatric lectures
Free registration

Nature Reviews Neuroscience
The November 2013 Nature Reviews Neuroscience includes a Viewpoint comparing the research advantages of the Research Domain Criteria (or RDoC) recently established by the US National Institute of Mental Health as an alternative nosology to the DSM series. While the DSM’s polythetic categories are convenient for clinical practice, there is growing evidence of a substantial overlap in the phenomenology and pathophysiology of syndromes treated as distinct entities in the DSM, such as schizophrenia and bipolar disorder. Specifically to facilitate research, the RDoC proposes five domains representing distinct brain systems which are disturbed in different ways in different psychiatric conditions. Casey and Lee state that the RDoC is intended to facilitate the translation of basic neuroscience findings to clinical diagnosis and treatment. The Viewpoint comprises the opinions of six leading psychiatric researchers comparing the research utility of DSM and RDoC approaches. Interesting arguments are proposed, such as Hyman’s
potential harm extended to brain stimulation devices to prevent that existing medical device legislation should be with no regulation or oversight.

Lancet services will be required to prevent systemic 4 million additional people with severe mental services already struggle to meet identified specialist teams. Olfson and colleagues also provision of lithium, clozapine, and employment improved a by the Affordable Care Act for pr

The October 2nd JAMA includes an editorial by Offson and colleagues advocating for greater investment in the expansion of collaborative care with mental health specialists collocating with primary care doctors. They describe opportunities arising within the structures established by the Affordable Care Act for improved and more efficient outcomes for patients with severe mental illness by the provision of lithium, clozapine, and employment services by primary care doctors supported by specialist teams. Offson and colleagues also point out that in the US specialist mental health services already struggle to meet identified needs. With the expansion of health insurance to 4 million additional people with severe mental illness by 2019, efficiencies or expanded services will be required to prevent systemic failure.

Lancet

The September 14 Lancet includes a letter by Maslen and colleagues observing that it is possible to order online brain stimulation devices such as transcranial direct-current stimulators with no regulation or oversight. They suggest that existing medical device legislation should be extended to brain stimulation devices to prevent potential harms.

COHERENCE AND PSYCHIATRIC GENETICS

Kendler and neurobiological coherence
Genetics of schizophrenia
Coherence in BPAD and ADHD
Shared genetic risk factors in psychiatric disease

In November, Australian Psychiatry Review examines recent progress in psychiatric genetics. The review uses Kendler’s review in Molecular Psychiatry as a starting point. Kendler describes growing confidence that with increasing power and demonstrated replications, results from GWAS and large-effect size rare genomic variants may lead to significant breakthroughs in understanding of psychiatric illness. He proposes that the value of this research will be determined by the level of biological coherence of genes and molecules implicated in psychiatric disease by genetic studies. This will depend upon how well the genes and molecules can be integrated into tangible mechanisms, such as metabolic pathways, neurotransmitter systems, and neurodevelopmental trajectories. If diverse
sources of evidence cohere into a manageable set of molecular mechanisms which map well onto phenomenology and syndromes. Kendler is confident that psychiatric genetics will provide critical insights into the underlying biology of psychiatric syndromes and allow us to understand the disordered relationships of the brain and mind.

The section will:

- first: summarise Kendler’s framework for understanding psychiatric genetics, including the importance of biologically coherent evidence across research domains
- second: illustrate Kendler’s framework using recent studies on the genetics of schizophrenia
- third: note an effort to facilitate coherence using an open database of genetic studies of bipolar disorder by Chang and colleagues
- fourth: refer to more speculative recent studies on the genetics of ADHD
- and fifth: conclude with reference to recent efforts to explore genetic risk factors shared between multiple psychiatric disorders

Kendler breaks psychiatric genetics down by study type. In the absence of recent advances in molecular genetic techniques, early genetic studies involved family, twin, and adoption studies, which provided evidence that all psychiatric disorders aggregate in families and are heritable. He notes that these studies are unable to prove that heritable disorders are biological, and therefore cannot support a coherent neurobiological understanding of psychiatric illness.

The first generation of molecular genetic studies included linkage studies, which assess the co-segregation of particular genetic loci with the presence of disease in families. Essentially, this type of study relies upon statistical analysis of the tendency of genes located on the same chromosome to be transmitted together from parent to child. Linkage analyses compare the frequency with which genetic markers actually occur in members of a genetically related group who are affected by a disease such as schizophrenia, to how frequently they are expected to occur. Genetic markers that occur more frequently than expected in patients with the disease are putative aetiological agents. Kendler notes that linkage analyses failed to demonstrate replicable mechanisms underlying psychiatric diagnoses or phenomenology. However, they did rule out the hopeful hypothesis that a few large-effect genes could explain the aetiology of psychiatric illnesses.

The next generation within molecular genetics moved from linkage analyses to genome-wide association studies (GWAS), which compare the frequency of genetic variants between people who have a condition of interest, to those who do not have the condition. DNA of each participant and controls is sampled and analysed using arrays capable of characterising the pattern of allelic variants for millions of genes. The huge number of tests massively increases the possibility of false positive or negative results, requiring enormous sample sizes for adequate power to confidently identify statistically significant effects. Early GWAS did not identify replicable genetic effects due to low power. However, with increasing sample sizes, replicable effects have emerged. At the same time, copy number variants (CNVs) that potentially encode multiple genes, and duplications of large sections of DNA substantially increase risk of specific psychiatric illnesses. Kendler suggests that a substantial proportion of genetic variation in

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**JAMA PSYCHIATRY**


**BIOLOGICAL PSYCHIATRY**

11. Steudte S, Kirschbaum C, Gao W, et al. Hair Cortisol as a Biomarker of Traumatization in Healthy Individuals and
psychiatric illness results from large numbers of small effect variants. He outlines the framework for translating knowledge about individual genes and genetic copy number variants affecting multiple genes into a coherent understanding of psychiatric illness. Genes operate at a biochemical level by the production of proteins. A coherent understanding of illness described at the level of patterns of behaviour will require translation of biochemical processes, through their effect on cellular dynamics, affecting neuronal networks, which comprise brain circuits which then directly control behaviour.

Kendler examines the possibility of different levels of coherence of neurobiological models of psychiatric illness emerging out of psychiatric genetics and related fields. He proposes that it is unlikely that these efforts will lead to no coherence or high coherence, and argues that it is more likely that our developing models will achieve moderate coherence. One pathway to moderate coherence for a particular disorder such as schizophrenia would be evidence linking dysfunction in a brain circuit subserving behaviour, such as the cortico-basal ganglia-thalamic loops, to abnormalities in any of multiple neuron types associated with specific neurotransmitter systems. Moderate coherence would arise out of the fact that multiple genes affect a common pathway through multiple highly variable mechanisms also affected by individual variation and interaction with environmental exposures.

Kendler thus provides a parsimonious framework for understanding the relevance of recent psychiatric genetic research.

Recent psychiatric genetics research in schizophrenia

Neatly illustrating the failure of past efforts in psychotic genetics to demonstrate coherent models of psychiatric illness, an editorial by Sullivan explores the history of the DISC1, or Disrupted in Schizophrenia structural genetic variant, first flagged as a potential causal agent in a subset of patients with schizophrenia 20 years ago.44 First discovered in 1970, DISC1 is associated with three structural variants, most commonly involving neurodevelopmental processes. Despite long intense investigation, the role of DISC1 remains equivocal, with some research groups believing it is an aetiological agent, some that it is not, and some that more data is needed to reach valid conclusions. Sullivan argues that progress in psychiatric genetics requires high quality research guided by rigorous standards, and that DISC1 is an example of research that is hopefully explored as 'intriguing' rather than confidently investigated with clear results.

More positively, Mowry and Gratten summarise an emerging spectrum of allelic variation in schizophrenia.45 Using GWAS across international consortia with ever-larger sample sizes, Mowry and Gratten describe a research effort combining genetic insights with cellular models, animal models, and imaging genetics. They propose that the genetics of schizophrenia lie somewhere between original models, described as common disease common variant models, which posited that one or a small number of genes would explain most of the variance; and more recent models, known as common disease rare variant models, which argue for extreme genetic heterogeneity involving many rare but highly penetrant mutations. Evidence from recent GWASs and related research suggests a spectrum of illness involving the interaction of large numbers of genes of small effect in some manifestations of schizophrenia, through to a small number of rare genes of large effect in other manifestations of psychotic illness. Mowry and Gratten echo Kendler’s optimism, though both articles emphasise that most of the work remains to be done.

Bipolar genetics database

An article by Chang and colleagues in the latest Biological Psychiatry summarises genetic evidence on bipolar disorder, candidate molecular pathways, and genetic factors potentially shared between bipolar disorder, major depressive disorder, and schizophrenia.46 Chang and colleagues note bipolar heritability of 80%, with clinical features such as psychosis and suicidality shared with depression and schizophrenia. They have constructed a publicly available database of this evidence including searchable results from 796 papers containing 797 candidate genes for bipolar disorder, with 447 genes with at least one positive finding. The most studied genes are SLC6A4, BDNF, and DRD2. They have also identified 245 pathways from GWASs, including calcium channel activity and central nervous system development. The majority of pathways were involved in synaptic transmission, membrane, and ion channel activity. Their searchable database focuses on identifying genetic factors with multiple sources of evidence, and facilitates testing of hypotheses regarding convergent pathways within and across disorders, which appears likely to foster Kendler’s idea of coherence.

Recent psychiatric genetics research in ADHD

Koenen and colleagues comment on the challenges and promise of genetic studies in post-traumatic stress disorder (PTSD).47 Noting that the tendency to PTSD is heritable, they review research that seeks to explain the vulnerability and resilience of people exposed to stress. Candidate gene studies use prior biological knowledge to identify possible genes underlying particular psychiatric phenotypes. They develop the example of Wilker and...
colleagues, which built on disturbed memory function in PTSD to justify the study of KIBRA, a memory-related protein. Wilker and colleagues found minor alleles of two single nucleotide polymorphisms (or SNPs) encoding KIBRA reduced the lifetime risk of PTSD in genocide survivors.

GWASs do not attempt to predict candidate genes, but rely on enormous sample sizes to detect associations between phenotypic and genotypic variation. Xie and colleagues found evidence for an association between Tolloid-like 1 gene and PTSD. 49

Candidate gene studies are currently out of favour because of high false positives and low replication rates, as well as inadequate biological knowledge to identify high-probability candidate genes. GWAS have located the majority of risk variants in non-coding regions of the genome. Consistent with Kendler’s criterion of coherence, Koenen and colleagues suggest both candidate gene and GWAS can contribute to an understanding of PTSD mechanisms. To this end they have established the PTSD working group within the Psychiatric Genomics Consortium to conduct very large analyses of candidate and GWAS of PTSD. They identify five main challenges in this endeavour, including how to identify and measure trauma load, defining the PTSD phenotype, managing comorbidity, population stratification for genotype distribution by ancestry, and appropriate sampling.

Psychiatric disorders with shared psychiatric risk factors

Finally, there has been growing attention to the probability of shared genetic aetiology across psychiatric disorders. An article by the Cross-Disorder Group of the Psychiatric Genomics Consortium is a recent example, reporting GWAS showing high correlations of SNPs between schizophrenia, bipolar disorder, major depressive disorder, ADHD, and Autism Spectrum Disorder. 50 These studies promise to expose common neurobiological mechanisms underlying the substantial overlap in phenomenology between conceptually distinct entities such as schizophrenia and bipolar disorder, reflected in the hybrid schizoaffective diagnosis, and in efforts to move from a categorical to a dimensional diagnostic system. The Cross-Disorder Group of the Psychiatric Genomics Consortium concludes that their work will motivate investigation of shared pathophysiologies and common therapeutic mechanisms.

Summary

Thus, a clarifying caricature of the current state of psychiatric genetics might note the identification of ever larger numbers of common gene variants with small, non-specific effects on psychiatric dysfunction, alongside rare genetic variants with large, specific effects on particular psychiatric disorders. There is a growing move towards large international consortia to facilitate the enormous sample sizes needed to achieve adequate power in GWAS. Kendler provides a framework based on coherence with which to structure research based on psychiatric genetics, and to evaluate the results. This framework suggests that psychiatric genetics continues to promise future breakthroughs rather than deliver present understanding, though Kendler, Mowry and Gratten, and the Psychiatric Genomics Consortium papers find grounds for optimism.

Conclusion

And that’s it for the November edition of Australian Psychiatry Review. Listeners directed to the podcast from the Royal Australian and New Zealand College of Psychiatry's CPD Online page can access questions for CPD points using the password “coherence”. See you next month!


FOCUS - COHERENCE AND PSYCHIATRIC GENETICS


NATURE REVIEWS. NEUROSCIENCE


JAMA


Lancet


BMJ


FOCUS - COHERENCE AND PSYCHIATRIC GENETICS


Two things fill the mind with ever-increasing wonder and awe, the more often and the more intensely the mind of thought is drawn to them: the starry heavens above me and the moral law within me. – Immanuel Kant, 1788

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