I’m Andrew Amos, and this is the September edition of Australian Psychiatry Review. This month closes with a focus section on optogenetics, an exciting technique that allows scientists to control genetically determined types of neurons with millisecond accuracy. Highlights from the psychiatric literature over the last month include debate in the Australian and New Zealand Journal of Psychiatry over the legal and clinical basis of abortion justified by increased risk of adverse mental health; articles in JAMA Psychiatry and Biological Psychiatry exploring evidence linking schizophrenia with disrupted connections between specific brain regions, with Fan and colleagues in Biological Psychiatry demonstrating that olfactory stem cells taken from adults with schizophrenia show adhesion and motility dysfunction that might explain neurodevelopmental abnormalities.

Australian Psychiatric Journals

ANZJP - September 2013

Editor Scott Henderson opens the September 2013 issue of the Australian and New Zealand Journal of Psychiatry noting the value and uncertainty of opinions, defined as judgements resting on grounds insufficient for complete demonstration. This is a useful reminder in an issue with evidence and interpretation of the merits and ethics of abortion. Ferguson and colleagues review evidence that abortion is unlikely to improve mental health risks of unwanted pregnancy, and may increase some risks. They link this to evidence that up to 90% of abortions in certain developed countries are authorised on the grounds that continuation of pregnancy would pose a serious threat to the woman’s mental health. Ferguson and colleagues draw the strong conclusion that there is no evidence to support the proposal that abortion has mental health benefits.

Separate viewpoints by Steinberg and Romans point out the limitations of necessarily descriptive data on abortion, which cannot establish causation, and likely miss relevant sub-groups at particularly high risk of poor outcomes. In his Editorial, Henderson notes that because of the ethical impossibility of controlled comparisons between women who are pregnant, and who seek, then either have, or do not have, an abortion, we will never be able to answer the question posed by Ferguson and colleagues. Steinberg highlights a paper by Gilchrist, the only extant research comparing women who underwent abortion with those who sought abortion but were denied, which found a higher rate of psychosis in women denied abortion.

Berk and colleagues highlight the gap between the prevalence and treatment of serious mood disorders, and recommend public health measures supporting collaborative care in general practice settings. Noting high rates of recurrence, they question whether episode-based treatment should be discarded in favour of a chronic-disease model of the treatment of depression. Berk and colleagues also suggest access to public mental health services should be expanded from the current risk-based assessment, to include those with severe and potentially treatable disorders even in the absence of critical safety issues. They acknowledge that the high prevalence of mood disorders necessitates funding focused on primary care, but argue that inadequate systems of training and coordinated care mean substantial numbers of patients who do not respond to SSRIs or CBT are missing out on potentially helpful specialised interventions. They suggest primary care for mood disorders should be supported by specialist services focused on capacity generation and upskilling in primary care staff, with more intensive hands-on care where possible.

The ongoing debate regarding early intervention in psychosis continues, with McGorry arguing in a letter that recent pessimism regarding the possibility of predicting and preventing the transition from subclinical to syndromal psychotic illness is unfounded. An associated letter by Jorm agrees with McGorry that CBT may be the most appropriate first intervention for people at risk of psychotic illness, while highlighting that recent interventions using antipsychotics in patients at high risk of psychosis raise ethical concerns.

Inside this issue:

2. International Psychiatric Journals
3. International Medical Journals
4. FOCUS SECTION – Optogenetics in Psychiatry
References


An article by van den Heuvel and colleagues in the August edition of JAMA Psychiatry reports structural diffusion tensor imaging and functional magnetic resonance imaging in patients with schizophrenia and healthy controls. Their analysis is motivated by a dynamic model which conceptualises the brain as a large-scale network of interconnected hub regions which integrate distributed cognitive processes. They found significant interruptions in the pathways connecting midline frontal, parietal, and insular cortical areas in patients with schizophrenia. They also noted that anatomical features connecting distributed nodes in patient brains determined more of the interactions between those areas than in healthy controls, suggesting more automatic and less dynamic brain function in patients. They link these results with models of psychosis involving ineffective integration of perceptual and intellectual information distributed throughout the brain. An editorial by Bullmore and Vertes link van den Heuvel’s work with modeling approaches, including the increasing use of graph theory to represent complex brain networks. Graph theory abstracts brain organisation as regional nodes connected by edges with measurable patterns of connectivity showing emergent properties such as small-worldness. A small-world network is one in which most nodes of the network are not connected with each other, but are reachable by a small number of intermediating nodes.

A viewpoint by Braff and Braff contrasts the rapid advances in neuroscientific knowledge with the slow pace of change in neuropsychiatric clinical practice. More rapid advances in translational medicine tend to occur where diseased tissue can be directly examined, such as solid tumours, while neuropsychiatric symptoms arise from less tangible disruption of complex neural circuits. They note the promising illusion of genetic testing for neuropsychiatric disease, with its abundance of genetic factors of very small effect, placed in perspective by the ongoing failure to generate any effective treatments even from the identification of the autosomal dominant Huntington’s gene, and suggest toning down overstated claims to avoid public disappointment.

An article by Martin and colleagues published online on August 28 reanalyses data from a national US survey and concludes that the traditional truisms that depressive illness is more prevalent in women is explained by different characteristic symptoms of depression in men and women. They suggest that prevalence rates of depression are equal when using scales that include externalising symptoms found at higher rates in men, including anger/aggression, substance abuse, and risk-taking. They consider different explanations of these patterns, including that men may be more willing to report externalising symptoms such as anger because they are less threatening to masculine ideals than traditional symptoms such as sadness and hopelessness.

Nelson and colleagues provide a long-term follow-up of ultra-high risk patients recruited to the PACE clinic in Melbourne, Australia between 1993 and 2006. Transition to psychosis was assessed in 416 patients between 2 and 15 years after presentation. The overall rate of transition was 35% over ten years, with the highest risk in the first two years. Factors associated with transition included year of presentation,
duration of psychosis prior to entry, baseline function, negative symptoms, and disorders of thought content. The authors conclude that services should follow patients at risk of psychosis for at least two years, with closer monitoring for people with longer duration of symptoms and poorer functioning at presentation.

Molecular Psychiatry
In September Molecular Psychiatry published a review by Taylor and colleagues of the vascular depression hypothesis, which proposes that cerebrovascular disease may interact with geriatric depression. They describe well-established relationships between late-life depression, vascular risk factors, and brain imaging abnormalities, including treatment resistant depression predicted by cognitive deficits. Taylor and colleagues propose a disconnection hypothesis where the specific site of vascular damage and white matter lesions determine depressive and cognitive symptomatology, more than globally distributed damage. They refer to research linking late-life depression with damage to neural tracts including the anterior thalamic radiation, cingulum bundle, uncinate fasciculus, and superior longitudinal fasciculus. They examine how inflammatory and hypoperfusion processes might influence the development of depression.

Biological Psychiatry
The 15th September Biological Psychiatry includes two articles reviewing the potential of oxidative stress measures and cortisol as state and trait markers for schizophrenia. Flatow and colleagues provide a meta-analysis of blood oxidative stress parameters in schizophrenia, including the effects of clinical status and antipsychotic treatment. They identify possible state markers for acute psychosis in antioxidant status, red blood cell catalase levels, and plasma nitrite levels, all elevated during acute episodes, while red blood cell superoxide dismutase may be a trait marker for schizophrenia, as it is abnormal in both stable and acutely unwell patients.

Walker and colleagues report data from a longitudinal multicenter trial examining cortisol in people at risk of psychosis and healthy controls. Cortisol was higher in those at-risk of psychosis, positively correlated with baseline symptom severity, and higher in those who transitioned to psychotic-level symptoms.

Triggered by evidence from genetic association studies implicating genes involved in neural migration in the aetiology of schizophrenia, Fan and colleagues reported that olfactory neural cells derived from patients with schizophrenia were less adhesive and moved faster than those of healthy controls. They biopsied the olfactory mucosa, which contains multipotent stem cells capable of neurogenesis throughout life, and used time-lapse imaging to assess cell motility and adhesion dynamics. The authors conclude that alterations in cell adhesion dynamics and cell motility could bias the trajectory of brain development in schizophrenia.

Khadka and colleagues examined functional brain connectivity in patients with schizophrenia, psychotic bipolar disorder, relatives of patients with schizophrenia or bipolar disorder, and healthy controls with no family history. They used resting state functional magnetic resonance imaging to assess regional interactions of brain circuits and found evidence of network abnormalities, most pronounced in schizophrenia, with a similar pattern in bipolar disorder, and less severe patterns in healthy relatives of those with mental illness. The authors speculate that there may be a continuous spectrum of circuit dysfunction from healthy controls without family history, through unaffected relatives, to those with mental illness, and discuss disrupted connections as potential endophenotypes of psychosis. They tentatively identify such endophenotypes in the disruption in three regional networks common to patients and their relatives but not healthy controls: fronto-occipital cortex, frontal/thalamic/basal ganglia, and sensorimotor networks.

Velligan and colleagues report a trial in which 142 patients in the maintenance phase of treatment for schizophrenia were randomised to usual treatment, in-person compliance support, or an electronic medication monitor that cues medication use, warns of errors, records complaints, and alerts treatment staff of non-adherence. Adherence was equivalent in both active treatments at 90-92%, significantly better than treatment as usual, at 73%. Better adherence was not associated with better outcomes.

International Medical Journals

JAMA, Lancet, BMJ

JAMA
The August 7 issue of JAMA is a themed issue on violence and human rights, with multiple articles relevant to psychiatrists. An editorial by Katherine Mills examines treatment of comorbid substance dependence and PTSD. Foa and colleagues report a RCT involving 165 patients with comorbid PTSD and alcohol dependence. They compared naltrexone, exposure therapy, or both, with supportive therapy. They show that naltrexone can reduce dependence behaviours without exacerbating PTSD symptoms. While exposure therapy did not affect trauma outcomes at the end of treatment, it did reduce relapse over 6 month follow-up, and may improve drinking outcomes. The combination of treatments was not superior to either treatment alone.

Crosby discusses the management of a refugee from the civil war in Somalia treated in the US for weakness, pain, and PTSD.
She describes a multidisciplinary, culturally acceptable approach, alongside evidence-based World Health Organisation guidelines for the management of patients exposed to trauma, violence, and large-scale disasters, with attention to countries with limited resources. Crosby includes specific instructions for interviewing refugees likely to have been exposed to violence, including questions about torture and recovery. van Ommeren and colleagues recommend therapy and advise against pharmacotherapy as first-line treatments for acute stress symptoms and PTSD in the absence of moderate to severe depression.25 Feder and colleagues summarise WHO recommendations regarding management of women exposed to intimate partner violence.26 The recommendation against screening all women for intimate partner violence is based on evidence that screening does not reduce intimate partner violence or improve women’s outcomes.

In the August 21 JAMA, President of the APA, Jeffrey Lieberman and colleagues announce the importance of early detection and intervention approaches to schizophrenia, noting the slower pace of reform in the US compared with other developed countries, due most likely to the difficulty of financing early detection and intervention in a system highly dependent on health insurance in the absence of universal health care.28

Lancet
A letter in the August 24 Lancet reports that the South Korean Neuropsychiatric Association has changed the term for schizophrenia from jungshingbunyeolbyung, or mind-split disorder, to johyeonbyung, or attunement disorder, to avoid the stigma associated with the earlier term preventing people from presenting for treatment.27 The letter notes that a similar change in 2002 in Japan did lead to increased presentations with psychotic illness, and reflects that the meaning of the new term is not self-evident to Korean speakers, but requires explanation, similar to the term schizophrenia when introduced by Bleuler.

BMJ
On the 19 August the BMJ published a cluster randomised trial by Richards and colleagues on collaborative primary care for depression in the UK.29 581 adults in 51 primary care practices allocated to collaborative or usual care showed better outcomes for the collaborative care group on a Patient Health Questionnaire-9 (PHQ-9) measure of depression at four and twelve months. Collaborative care was delivered by care managers under the supervision of mental health specialists.

That’s it for the monthly roundup, next we look at optogenetics in psychiatry.

Optogenetics in Psychiatry

Optogenetics is a set of novel neuroscience techniques developed over the last decade that render genes and proteins in nerve cells responsive to light. Essentially, scientists modify receptor genes expressed in specific types of neurons so that they or their protein products can be selectively activated or inhibited by the application of light. Deisseroth presents a non-technical overview in Scientific American,30 while a review by Fiala and colleagues in Current Biology in 2010 describes various optogenetic techniques in more detail.31 Collectively these techniques answer the major challenge for neuroscience identified by Francis Crick in 1979, the need to control one type of cell in the brain while leaving others unaltered.32

The main points established by this feature are:


---

- optogenetics combines genetic engineering of protein expression with light-sensitive protein molecules to control the firing of genetically determined sets of neurons
- particular ion channels used in optogenetics to activate or inactivate neurons include P2X2 and the channelrhodopsins
- optogenetics has most commonly been used in animal models such as drosophila melanogaster, or fruit-fly models
- by activating or inactivating specific sets of neurons, optogenetics has refined previous models of reward by identifying how specific groups of cells in the amygdala, ventral temporal area, and nucleus accumbens interact when animals learn a conditioned fear response
- optogenetics promises control over subcellular units such as vesicles, gene transcription, and endoplasmic reticulum

**Basic optogenetic techniques**

Fiala and colleagues outline basic optogenetic approaches. One technique used in research with drosophila melanogaster, a common animal model of neural mechanisms, causes an ion channel protein, P2X2, to be expressed in specific neuron populations. The channel protein remains closed until it is bound by a specific ligand, ATP. Researchers then inject ATP bound by a light sensitive molecule which prevents binding to P2X2. They are then able to selectively activate genetically defined neuron populations by opening the P2X2 channel with strong UV light, which releases ATP for binding, causing specific neurons to fire.

Another technique involves conjugating a light-sensitive molecule to an ion channel in a neuronal membrane. Varying the wavelength of light changes the conformation of the light-sensitive molecule, fixing the channel open or closed, activating or inhibiting the neuron.

A particularly common technique uses channelrhodopsins isolated from green algae. Rhodopsins are cation channels which bind to all-trans retinal, a chemical that makes the channel sensitive to blue light. This protein is particularly useful because the channel can be opened and closed with light flashes of milliseconds duration similar to the time-frame of neuronal membranes during action potentials.

As it requires genetic modification and access to brain tissue, optogenetics research is currently limited to animal models. Nevertheless, in May Current Opinion in Neurobiology published online a review of implications of optogenetics for psychiatric diseases. They summarise optogenetics research on brain circuits involved in sleep, arousal, fear, and social and aggressive behaviour.

Sleep researchers have made strong use of optogenetics. Sleep and arousal arise from complex interactions between multiple populations of cells distributed throughout the brain. Optogenetic techniques have been applied to orexin secreting cells in the lateral hypothalamus and noradrenergic cells in the locus ceruleus. Both orexin and noradrenaline increase arousal. Direct optical stimulation of orexin releasing neurons increased the probability of waking in a frequency-dependent manner, while stimulation of locus ceruleus neurons caused immediate waking in sleeping animals.

Optogenetics is proving particularly useful in dissecting the neuronal pathways associated with reward seeking in animal models of addiction, including the mechanisms of brain circuit adaptations after exposure to drugs of abuse. Russo and Nestler provide a targeted review of reward circuits involved in mood disorders in Nature Reviews Neuroscience. The basic reward circuit in the human brain involves dopaminergic neurons in the ventral tegmental area of the midbrain, which project to the nucleus accumbens (NAc), a ventral part of the basal ganglia. These neurons consistently release small amounts of dopamine, called tonic stimulation. Acute increases in dopamine, or phasic release, have been thought to signal rewarding or salient stimuli, allowing learning to selectively increase or decrease behaviours associated with particular stimuli.

Optogenetics has allowed researchers to demonstrate that VTA DA neurons respond to reward outcomes while VTA GABA neurons are sensitive to predicting cues. Mice self-stimulated cells in the basolateral amygdala, but not the prefrontal cortex, while silencing basolateral amygdala afferents to the NAc reduced reward associated behavioural changes. These results suggest that VTA DA neurons and glutamatergic neurons from the basolateral amygdala facilitate reward seeking by activating DA sensitive neurons in the NAc, while VTA GABA neurons and inhibitory cholinergic interneurons in the NAc decrease reward-seeking behaviour by inhibiting DA sensitive neurons in the NAc.

While traditional neuroscience techniques allowed a basic description of the brain circuits underlying fear and anxiety, optogenetics has produced a more detailed understanding. Researchers have examined how stimulating or inhibiting specific neurons in the amygdala interferes with fear conditioning. For example, they have shown that optogenetic activation of pyramidal neurons in the lateral amygdala paired with a sound can induce fear conditioning in the same way as pairing an aversive stimulus like footshock with a sound. Other optogenetic studies have shown that there are two
populations of inhibitory GABAergic interneurons in the central nucleus of the amygdala which differentially respond to conditioned aversive stimuli, such as the tone that comes to be feared after being paired with a footshock. Interaction between these two sets of cells determines freezing behaviour in response to the tone. Taken together, these results suggest that the lateral amygdala integrates information about conditioned and unconditioned stimuli, while the central nucleus of the amygdala elicits the conditioned response of freezing.

Deisseroth and colleagues have begun to examine the mechanism of deep brain stimulation in treatment resistant depression and other psychiatric illnesses. Optogenetics allowed them to show that therapeutic effects of DBS applied to the STN are mediated by afferent axons arising from other regions rather than cell bodies in the STN.

The optogenetics repertoire continues to expand. Welberg, in Nature Reviews Neuroscience, describes new techniques allowing light-induced inhibition of vesicular release into synapses, and control of gene transcription and chromatin modifications. Another article by Deisseroth outlines extensions of optogenetics allowing selective activation of larger sets of neurons, including neurons defined by their projections, as well as general electrical and biochemical control of all non-nervous system cells in the body. Deisseroth suggests the next step will be specific control of subcellular units such as endoplasmic reticulum, kinases, and transcription factors, leading to an unprecedented level of control of cellular and subcellular processes.

A quiz with associated Continuing Medical Education points is available to listeners accessing this podcast through the Royal Australian and New Zealand College of Psychiatrists’ Continuing Professional Development page. To access the quiz you will need to enter the word “light” and follow instructions.

And that’s it for the September edition of Australian Psychiatry Review. See you next month!


**Online lectures**
http://www.paulmorrison.org/psychosis-research-where-have-we-been-where-are-we-going
- lectures at Institute of Psychiatry at The Maudsley; Sir Robin Murray’s lecture exploring myths of psychiatry, such as ventriculomegaly in schizophrenia, is particularly interesting.
http://psychiatry.yale.edu/education/grand/index.aspx
- Lectures for Yale Psychiatric Residents
http://streaming.biocom.arizona.edu/categories/?id=14
- University of Arizona Psychiatry Resident Grand Rounds; excellent series over several years
http://lms.mghacademy.org/Users/ActivityList.aspx
- Massachusetts General Hospital CME videos – requires free registration; covers Psychiatry and several other specialties
http://www.charlierose.com/watch/60057020
- Charlie Rose special on schizophrenia, co-hosted by Eric Kandel (co-author of Principles of Neural Science)
http://www.charlierose.com/watch/60073097
- Charlie Rose special on autism, co-hosted by Eric Kandel (co-author of Principles of Neural Science)
http://www.charlierose.com/watch/60160027
- Charlie Rose special on PTSD, co-hosted by Eric Kandel (co-author of Principles of Neural Science)
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

Dr Andrew Amos

Early Psychosis Gold Coast
Robina Hospital
2 Bayberry Lane
Robina, QLD, 4226