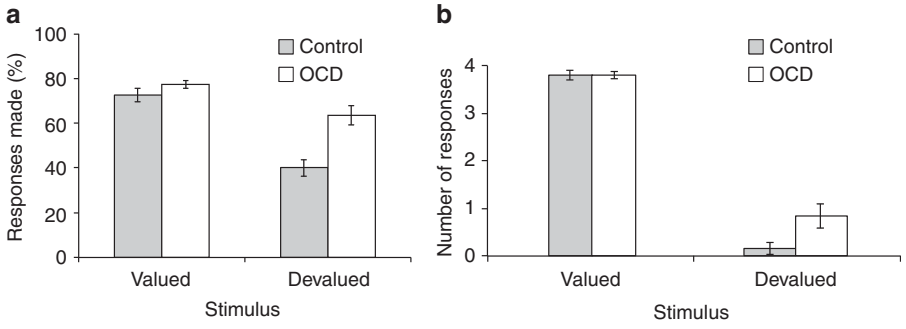

Figure 1. Excessive habit learning in OCD. Data reprinted with permission from Gillan *et al* (2011, 2014a). (a) OCD patients show excessive habit learning index by way of elevated responses towards devalued outcomes following appetitive instrumental learning. There was no group difference in responding for valuable outcomes (Gillan *et al*, 2011). (b) Over-active habits are also observed following aversive learning in OCD (Gillan *et al*, 2014a). Error bars denote standard error of the mean.

extinguish fears that accompany normal intrusive thoughts and worries. In support of this, impairments in extinction recall are evident in OCD, and the respective neural correlates also overlap on regions thought to be involved in the disorder (Milad *et al*, 2013). However, patients with post-traumatic stress disorder (PTSD), for example, have similar deficits in fear-extinction recall, but do not typically present with obsessions. In this light, fear-conditioning abnormalities in OCD may more parsimoniously reflect concomitant anxiety in OCD, rather than obsessions.

If not a dysfunction in fear extinction, what are obsessions in OCD? One possibility is that they are not an underlying trait in OCD, but instead an agitated mental urgency, or cognitive instantiation of more abstract feelings of anxiety and compulsive urges. A more elaborated view is that obsessions in OCD might arise as a result of compulsive behaviour. When trying to explain their bad habits, in the avoidance habit study described above, some OCD patients fell foul of reverse inference, erroneously deducing that if they felt driven to perform an act of (habitual) avoidance, they must have had something to fear (Gillan *et al*, 2014a). Studies have shown that with continued avoidance normal, albeit faulty, beliefs about threat cannot extinguish (Lovibond *et al*, 2009). It is plausible in this light that we have been thinking about OCD backwards: perhaps compulsions are a core feature of the disorder and obsessions are a troublesome by-product.

ACKNOWLEDGEMENTS

Dr Gillan and Professor Sahakian are affiliates of the Behavioural and Clinical Neuroscience Institute, which is supported by a joint award from the Medical Research Council and Wellcome Trust (G00001354). Dr Gillan is supported by a Sir Henry Wellcome Postdoctoral Fellowship (101521/Z/12/Z). Professor Barbara Sahakian consults for Cambridge Cognition, Servier and Lundbeck. She holds a grant from Janssen/J&J. She has share options in Cambridge Cognition. Much of this research was funded by a Wellcome Trust grant awarded to T.W. Robbins, B.J. Everitt, A.C. Roberts, J.W. Dalley and B.J. Sahakian (089589/Z/09/Z).

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FUNDING AND DISCLOSURE

The authors declare no conflict of interest.

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Neuropsychopharmacology Reviews (2015) **40,** 247–248; doi:10.1038/npp.2014.201

Induced Pluripotent Stem Cell (iPSC) Models of Bipolar Disorder

Bipolar disorder (BP) is a progressive, life-threatening condition characterized by alternating episodes of severe depression and mania, ranked by the WHO as among the leading causes of lifetime disability. The heritability of BP is estimated at 85–95%, and genetic susceptibility loci, each with small effects, are emerging. Accumulating evidence suggests a developmental origin for BP: neuroanatomical abnormalities are often present at the first episode; there are organizational and neuronal migration alterations, with minimal astrogliosis. In addition, BP is typically diagnosed at adolescence when there is a shift from relying on earlier-developing brain regions to later-maturing prefrontal structures—a period when the brain may be particularly vulnerable to pre-existing neuropathologies (Strakowski, 2012). Since subtle changes in differentiation can produce neurological consequences that only become apparent much later in life, a developmental model to study BP is required.

The ability to reprogram adult somatic cells to induced pluripotent stem cells (iPSC) by expressing four transcription

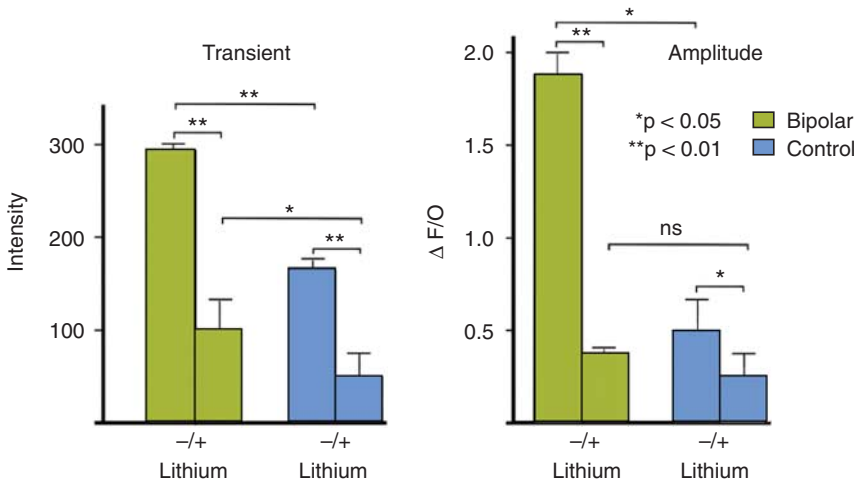

Figure 1. Changes in Flo-4AM fluorescence intensity and wave amplitude in control and bipolar neurons + Li.

factors found in the blastocyst inner cell mass and embryonic stem cells (Takahashi *et al*, 2007) now makes it possible to derive BP patient-specific stem cells. iPSC are well suited to identify alterations in cell behavior, examine gene expression, and identify novel signaling pathways in the affected cell type(s). In BP, they provide a robust source of cells from individuals with longitudinal observations, individuals on or off medications, and patients who have comorbid diagnoses, multiple episodes and treatments, unlike embryonic stem cells. iPSC have been derived for other neuropsychiatric disorders (e.g., Brennand *et al*, 2011), and are now being reported for BP.

We have derived iPSC lines from six BPI patients and six healthy control (C) individuals and differentiated them into neurons to study their morphology, signaling characteristics, and transcriptome. We have shown that calcium signaling is altered in BP neurons (Chen *et al*, 2014). Importantly, these cells can be used to examine responsiveness to pharmacological interventions, as lithium pretreatment reverted wave amplitudes to control levels (Figure 1).

These studies also indicated that BP neurons expressed transcripts characteristic of early ventral CNS fate: NKX2-2, FOXP2, ASCL1, LHX6, while control neurons expressed genes associated with dorsal telencephalic patterning: EMX2, FEZF2, PAX6, TBR2, TCF3, VGLUT1. Consistent with these results, prior to differentiation, control iPSC expressed significantly higher levels of LEFTY1,2 (which inhibit Nodal signaling) and of transcripts that regulate Hedgehog signaling, HHIP, and KIF7 (Cheung *et al*, 2009), which would promote dorsal telencephalic fate. Comparison of BP and C neurons also identified alterations in key components of the microRNA processing pathway, DICER and DROSHA, and of the mTOR pathway, RICTOR.

iPSC offer the first opportunity to study viable patient-derived neurons with the goal of understanding the molecular mechanisms underlying BP. We hypothesize that in BP neuronal cell fate determination is altered, increasing susceptibility to later epigenetic modifications. While iPSC provide important opportunities to model BP, much work remains to be carried out in larger family studies, to determine when during differentiation alterations may occur, and the cell types involved. This approach is beginning to identify novel, targetable signaling pathways in BP, and should provide the opportunity to identify and test effective medications for individual patients.

ACKNOWLEDGEMENTS

This work is supported by the HC Prechter Bipolar Research Fund and Steven Schwartzberg Memorial Fund at the University of Michigan.

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FUNDING AND DISCLOSURE
Dr O'Shea serves as a consultant for Genentech, Inc. Dr McInnis declares no conflict of interest.

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Neuropsychopharmacology Reviews (2015) **40,** 248–249; doi:10.1038/npp.2014.221

Brain Biomarkers of Treatment for Multi-Domain Dysfunction: Pharmacological fMRI Studies in Pediatric Mania

It is well established that pediatric bipolar disorder (PBD) not only presents with affected dysregulation but also cognitive difficulties in working memory, attention, verbal memory, and executive functional domains (Pavuluri *et al*, 2009). Neural circuitry abnormalities that explain this multi-domain dysfunction (Pavuluri, in press) have led to the pursuit of how such abnormal pathophysiology can be reversed with pharmacotherapy (Mayanil *et al*, 2011). We conducted the first series of