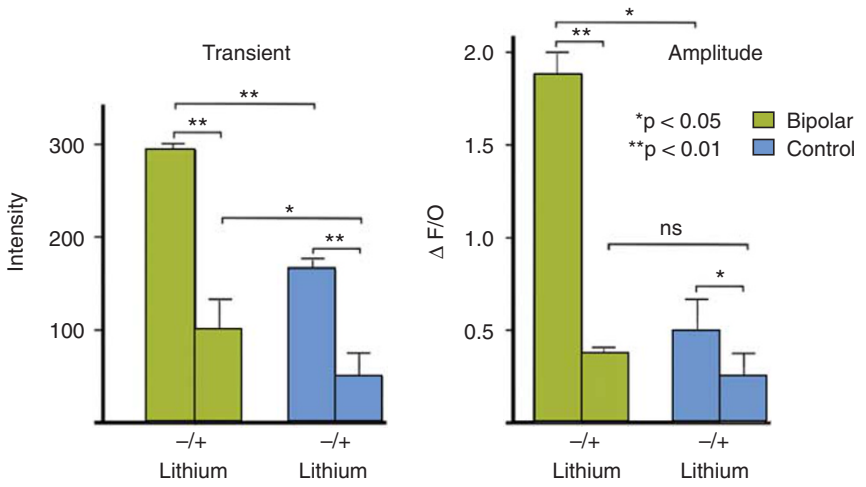

Figure 1. Changes in Flo-4AM fluorescence intensity and wave amplitude in control and bipolar neurons + Li.

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

fMRI studies in pediatric mania by examining the effects of lamotrigine, risperidone, and divalproex sodium (DVPX) individually as well as through a pharmacotherapy algorithm. The pharmacological fMRI studies used tasks to probe the domains of emotion processing, response inhibition, and the interface of emotion and cognition. Biomarkers of pharmacotherapy response, especially the increase in ventrolateral prefrontal cortex (VLPFC) activity in PBD relative to the healthy controls (HC), have been tied to the reduction in manic symptoms regardless of any task (Mayanil *et al*, 2011). Most studies summarized here were conducted on adolescents suffering from hypomanic state at baseline and are illustrated in Figure 1.

In the response inhibition and impulse control domain, using the stop signal task, lamotrigine increased the medial prefrontal cortex (MPFC), pregenual, subgenual, and posterior cingulate activity (PCC) in PBD over 14 weeks, while striatal activity was increased in HC. Lamotrigine's glutametergic attenuating action is associated with reduction in bipolar depression, where MPFC, DLPFC, striatum, and PCC showed increased activation from the baseline (Chang *et al*, 2008). Another double-blind randomized trial using independent-component analysis, compared the change in connectivity of brain circuits with DVPX *vs* risperidone in PBD and HC. Here, DVPX increased the connectivity of the subgenual cortex within the affective evaluation and inhibition circuitry during response inhibition. This is similar to the earlier outcome with lamotrigine, confirming the role of subgenual cortex during impulse control with an antiepileptic agent. However, antipsychotic risperidone is associated with increased engagement of insula relative to DVPX group or HC.

At the interface of working memory and affective processing domains, using the N-Back working memory task, relative to HC, patients with PBD showed increased activation response in subgenual cingulate and ventral striatum when risperidone was administered. The VLPFC–MPFC and medial temporal regions showed greater activity with lamotrigine as well as DVPX (the two antiepileptic agents) relative to baseline while patients were remembering angry faces.

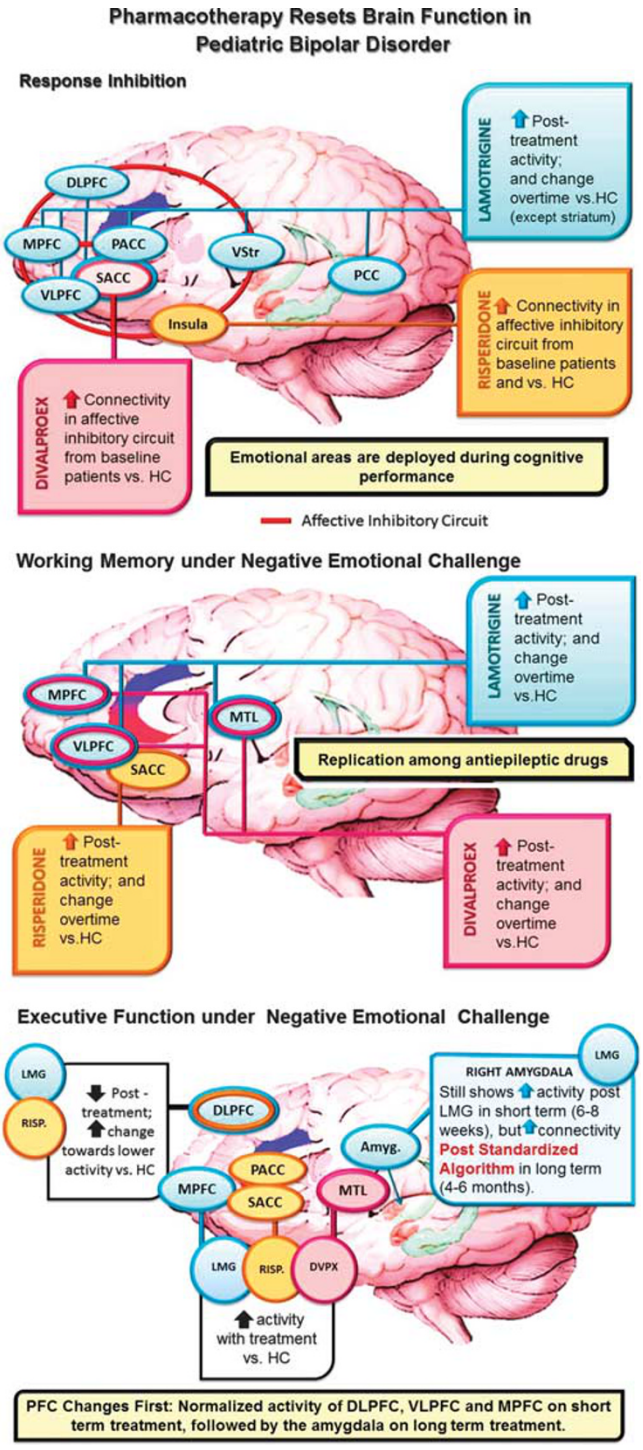

Figure 1. Medication works on brain to stabilize mood regulation. DLPFC, dorsolateral prefrontal cortex; MPFC, medial prefrontal cortex; MTL, medial temporal lobe; VLPFC, ventrolateral prefrontal cortex; VStr, ventral striatum; PACC, pregenual anterior cingulate cortex; PCC, posterior cingulate cortex; SACC, subgenual anterior cingulate cortex.

At the interface of executive function and affective processing domains, evaluative MPFC and ACC were engaged during negative word matching with all drugs, that is, risperidone, DVPX, and lamotrigine. However,

under the negative emotional challenge, cognitive DLPFC activation response was reduced with lamotrigine and risperidone. This explains the possibility that cognitive enhancers may be needed post-mood stabilization, based on medications used or to improve the residual attention difficulties intrinsic to PBD (Pavuluri *et al,* 2009). Furthermore, prognostic markers of clinical outcome began to emerge, with greater amygdala activity at baseline being a marker for poor outcome in the case of risperidone (possibly involving greater effort to subdue the amygdala), whereas greater MPFC activity was a marker for a good outcome (a sign of greater deployment of higher cortical region) in the case of DVPX, on direct comparison of these medication groups. Overall, these results indicated three things: (1) negative or angry stimuli were more successful in eliciting drug-related activity than happy or neutral faces in probing group differences; (2) medications differentially engaged the brain circuitry based on neurochemistry and tasks; and (3) state *vs* trait: with all medications, the amygdala showed reduced activity from baseline along with recovery from manic state, but remained active relative to that of HC (trait marker), while the PFC regions were normalized with mood stabilization (state marker). However, long-term treatment for at least 4 months with a standardized algorithm led to increased amygdala connectivity (Wegbreit *et al*, 2011) in the affective circuitry and normalized subcortical activity (Yang *et al*, 2013).

In summary, in PBD, multiple domains are malfunctioning at baseline. Combination of treatments such as coupling mood stabilizers with antipsychotics for severe episodes of mania may be useful as each type of medication engages different brain circuits.

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FUNDING AND DISCLOSURE

Dr Pavuluri receives or has received grant support from the following sources: National Institutes of Health (NIH), the National Institute of Mental Health, the National Alliance for Research on Schizophrenia and Depression (NARSAD), the American Foundation for Suicide Prevention, and the Marshall Reynolds Foundation. She is the recipient of the Berger-Colbeth Term Chair in Child Psychiatry and participated in the Otsuka Pharmaceuticals National Advisory Board meeting once.

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Neuropsychopharmacology Reviews (2015) **40,** 249–251; doi:10.1038/npp.2014.229

Mutual Information in a MEG Complexity Measure Suggests Regional Hyper-Connectivity in Schizophrenic Probands

Abnormalities of regional brain functional connectivity have been suggested for the syndromes of schizophrenia since the origin of the name using the Greek roots: *skhizein* (to split) and *phren* (mind) by Eugen Bleuler in 1908 (Kuhn, 2004). The neuropsychologist Norman Geschwind generalized this pathophysiological concept in his classic papers about what he called the *disconnexion syndromes* (Geschwind, 1965). He suggested that deficits in higher functions resulted from the disruption of pathways involving the signal relay functions of the association cortices. Discontinuities in white matter observed in *diffusion tensor imaging* and inferences from fMRI have been interpreted as evidence for cortical network disconnections in patients with schizophrenia (Bullmore *et al*, 1997).

More dynamical approaches to functional pathophysiological connections between brain regions have assessed their nearly simultaneous mutual similarities in frequency, wavelength, and phase (Uhlhaas and Singer, 2006). In addition, analysis of the envelope of oscillatory activity has yielded additional measures of connectivity. However, the brain does not operate by copying information from one region to another. The more general approach is to observe how broadband electrophysiological activity in one region shares information with other regions. To accomplish this we have expanded on our previous work using nonlinear dynamical measures of complexity for cortical activity (Robinson *et al*, 2012; Mandell, 2013).

A unique non-parametric measure of dynamical complexity, the symbolic *rank vector* approach (Robinson *et al*, 2012), was invoked to characterize the activity of the *beamformer localized*, time-dependent sources of the resting 275-channel whole-head magnetoencephalogram (MEG). MEG is the magnetic counterpart of EEG and has the advantage of yielding measures of cortical activity that are nearly independent of intervening conductivities. The source time series for an array of voxel locations is estimated from the multi-channel measurements using a linearly constrained minimum variance beamformer (Robinson and Rose, 1993). Each voxel time series is then converted to a symbolic time series by ranking their source magnitudes within a short *n*-place moving window. A measure of shared information, symbolic mutual information (SMI), is then computed for all voxel pairs from the probability of occurrence of their symbolic states (see Kraskov *et al*, 2004).

Subjects were recruited nationwide as part of an ongoing family study of schizophrenia at the Clinical Brain