Published in final edited form as:

Biol Psychiatry. 2017 November 01; 82(9): 621–622. doi:10.1016/j.biopsych.2017.08.019.

Timely Research in Bipolar Disorder and Attention Deficit Hyperactivity Disorder

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Keywords

Bipolar Disorder; Attention Deficit Disorder with Hyperactivity; Adolescent; Child; Attention; Risk

Two “timely” articles in the current issue of *Biological Psychiatry* provide novel evidence for cognitive, neural and genetic mechanisms that may underlie attentional disturbances in bipolar disorder (BD), and that directly or indirectly may help to clarify their overlap with those of attention deficit hyperactivity disorder (ADHD). The challenges of differential diagnosis between BD and ADHD, especially in youth, have drawn considerable focus, not least as the symptomatic expression of attentional deficits, such as distractibility, appear in both disorders within current nosological frameworks. The two studies in the Journal highlight the importance of researching the temporal dimension, at ‘macro’ and ‘micro’ levels, to elucidate the pathophysiologies underlying the disorders and parse successfully aspects that are common, and those that are unique to each disorder.

Time ‘macroarchitecture’

A temporal perspective, on the order of years, is pivotal to our understanding of mechanisms underlying attentional symptoms pertaining to multiple disorders, here, specifically ADHD and BD. The increased ability to adaptively focus and sustain attention is a core facet of prepubertal development. Impaired development of these attentional skills is a major driver of bringing school-aged children to clinical attention especially as it disrupts school-, home- and peer-related functioning. Thus, if attentional dysfunction is a component of a developmental psychiatric illness, the attentional component may be recognized in childhood. There are many potential neurobiological pathways to anomalous attentional functioning including altered developmental trajectories of ‘top-down’ cortical control

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Conflict of Interest Disclosures: The authors report no biomedical financial interests or potential conflicts of interest.

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systems or ‘bottom-up’ motivational-arousal systems. However, the extent to which specific aspects of attention and their underlying neural systems differentially contribute to the inattention of specific disorders is not clear. Possibilities include the involvement of different specific brain systems and associated attentional features. Alternatively, the attentional symptoms may be non-specific and thus a cross-sectional view of the attentional symptoms alone may not be sufficient to distinguish disorders. A longitudinal view of attention and/or other symptoms may be necessary to establish discriminative predictive power. Temporal views into early adulthood may also help distinguish the disorders, as ADHD symptoms tend to diminish or be relatively constant, whereas symptoms of BD are more likely to progress.

Time, on the order of weeks to months, is also key in differentiating neuropsychiatric disorders as time alone can distinguish chronic symptoms from episodic ones. While attentional symptoms are chronic in ADHD, they tend to be associated with episodes in BD with distractibility prominent during mania and inattention prominent during depression. However, symptoms can fluctuate in ADHD and the episode distinction may be more blurred in youths as younger individuals with BD tend to have more chronic symptoms. In adults with BD, attentional dysfunction, albeit less severe than in acute episodes, often persists during euthymia.

Recent trajectory and path analyses of symptom trajectories in BD point to the importance of the temporal dimension of symptoms, so far primarily with symptoms other than attentional, both in predicting BD onset and in disambiguating ADHD from BD. Trajectories of (hypo)manic symptoms appear particularly salient. A recent report suggests that symptoms of anxiety, depression and affective lability are often present for years prior to and persist in fully syndromic BD, while manic symptoms increase closer to the emergence of the full syndrome (1). A consideration of the trajectory of (hypo)manic, rather than purely attentional symptoms, is also supported by the recent finding that offspring with ADHD, with parents who did or did not have BD, did not differ in six-year trajectories of inattention (2). Thus, delineating the trajectory of subsyndromal manic symptoms may be more informative than mapping the trajectory of attentional symptoms. In this regard, in considering risk for transition to BD, it may be important to assess early, non-impairing hypomanic symptoms. The early detection of youth destined to grow into BD or to have persistent ADHD could inform primary prevention. For example, recent evidence suggests that psychosocial interventions, including the psychoeducation of family-focused therapy or daily rhythm regularization of interpersonal and social rhythm therapy, may improve outcome including reducing rates of converting to BD (3,4).

Time ‘microarchitecture’

Pagliaccio et al. (5) provide evidence for the intriguing possibility that time, on the order of milliseconds -the ‘micro-architecture’ of time- can be used to dissect complex entities such as attention to facilitate mapping onto pathophysiologically salient neural circuits. They report that intrasubject variability in response time (ISVRT), considered a marker of momentary lapses of attention, was increased in those with BD, even when euthymic, and in unaffected youth at familial risk. This trait cognitive anomaly was further associated with

blunted activation of fronto-striatal attention networks, both immediately prior to and after responses. The success of this study rested on its elegant use of trial-by-trial modelling of millisecond level variations in response time related to brain function. Indeed, the analytic approach of averaging brain activity across all trials did not reveal overall BD-related differences, thus missing an important neural anomaly. Notably, an increased ISVRT has also been reported in ADHD, but studies show the underlying neural anomaly is the intrusion of the attentional default mode network into active task-related processing (6,7). This supports the possibility of different neural mechanisms in BD and ADHD underly their grossly similar attentional deficits.

Can specific microarchitectural mechanisms of cognition, such as those elucidated by Pagliaccio et al. (5), help predict the temporal macroarchitecture of BD or ADHD, for example aiding the determination of whether a child with attentional difficulties has ADHD or will develop BD? Or might this early attentional feature represent a faulty foundation from which other cognitive anomalies emerge with age, taking ever more specific, symptom-causing forms (8)? Ultimately, longitudinal data must be assessed across different cognitive constructs over the dimension of time to understand the prognostic utility of a cognitive metric such as ISVRT and its status as a possible causal mechanism.

Developmental time also features prominently in the genetic study by van Hulzen et al. (9). This study powerfully demonstrates the rich insights that can be gained from harnessing the large, and ever-growing, shared genomic data in the Psychiatric Genomics Consortium. It is an exciting time in ADHD genomics with the discovery by this Consortium of the first genome wide significant variants. This will undoubtedly lead to the discovery of more shared and specific risk factors for ADHD, BD and indeed other disorders. The current study reports considerable overlap in the aggregate genetic risk for BD and ADHD, and reports novel, genome-wide significant risk variants that emerge when the disorders are analyzed together rather than separately. The authors also astutely conducted additional analyses restricting the BD subjects to a subgroup with an age of onset at or under 21 years. They found that amount of variance in the BD phenotype explained by genetic variation (as measured in this study) fell from 12% for the entire BD group to around 7% for the subgroup with an early onset. Further, the specific genes implicated by the most significant genetic signals also differed: in analyses of all BD subjects the shared risk genes have as yet undetermined functional roles, whereas the gene emerging when considering the early onset BD (*ADCY2*) implicates intracellular adenylate cyclase signaling. This cross-disorder study points to a ubiquitous cellular process as a possible mechanism for the overlap of ADHD and early onset BD.

The finding by van Hulzen (9) and colleagues of different risk genetic variants in analyses stratified by age of onset reminds that genes do not just confer 'static' risk for a disorder. Some genetic risks unfold in a developmental context. This is exemplified by longitudinal twin studies showing that the genetic risk for the onset of ADHD differs substantially from genes determining its outcome (10). Longitudinal data mapping symptoms and underlying neurocognitive trajectories are needed in order to access these 'trajectory' genes.

A fruitful time ahead

This is an exciting time for psychiatry when emerging technologies will provide temporal views not before possible, providing new research insights and modes of clinical care. A major challenge for the field has been developing animal models for psychiatric disorders. New models may more closely resemble psychiatric syndromes as consideration of time patterns is increasingly incorporated. In humans, brain functioning can be measured and altered along a wide spectrum of temporal resolution with new imaging and stimulation techniques. Temporal characteristics of human symptoms and behaviors can be modeled through the use of mobile technologies and big data analytics. These approaches benefit from collecting data on responses to ‘real-world’ stimuli with ‘real-world’ timing that are more ecologically valid than laboratory-based paradigms. Thus, we may be headed to an era when ability to understand and leverage time may provide a leap forward in understanding, treatment and prevention of psychiatric illnesses.

Acknowledgments

PS is funded by the intramural programs of the national human genome research institute and the national institute of mental health. HPB was supported by research grants from the National Institute of Health (NIH) R61MH111929, R21 MH108940, R01 MH113230, RC1MH088366, R01MH070902, R01MH069747, RL1 DA024856; International Bipolar Foundation; Brain and Behavior Research Foundation; American Foundation for Suicide Prevention; and Women’s Health Research at Yale.

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