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RUNNING HEAD: Socio-emotional Functioning in Bipolar Disorder

Socio-emotional Functioning in Bipolar Disorder Versus Typical Development: Behavioral and Neural Differences

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Abstract

Socio-emotional dysfunction is a core feature of bipolar disorder (BD) across the lifespan. Recent evidence indicates associations between this atypical functioning and the presence of neurally-based anomalies. This article critically reviews the literature on two types of core socio-emotional skills that may represent endophenotypes for BD, with a focus on differences between individuals with BD, both youth and adults, and their typically developing peers. First, it examines studies of social cue perception and interpretation, with an emphasis on behavioral and neural studies of facial expression processing. Second, it shifts to examine behavioral and neural differences in cognitive and behavioral flexibility. Finally, the article summarizes potential future directions for research in this area.

Findings from a burgeoning literature converge to indicate neurally-mediated socio-emotional dysfunction relative to psychiatrically typical peers in individuals with bipolar spectrum disorders (BD) across the lifespan. Elucidating this dysfunction and its relationship with specific behavioral deficits or endophenotypes and their neural underpinnings may help inform our understanding of both psychopathological and typical development. Knowledge about how development in the context of BD deviates from the norm may also facilitate further creation and refinement of effective interventions.

This article reviews select aspects of socio-emotional development as they relate to BD, with particular focus on how socio-emotional functioning in the context of BD does or does not deviate from typical patterns. Although it would also be useful to compare patterns of function between youths with BD and those with other psychological disorders, such as Attention Deficit Hyperactivity Disorder (ADHD) or Major Depressive Disorder (MDD), few studies to date provide data on socio-emotional functioning and/or its neural correlates in multiple clinical groups. Thus, although this article highlights studies that include direct comparisons of clinical samples, the literature remains too small to permit a thorough review focused on BD as it resembles and differs from other psychological disorders.

It is important to note that the reviewed studies vary along several key parameters, rendering some direct comparisons among them difficult. First, reflecting ongoing controversy about how best to diagnosis BD in youths (Youngstrom, Birmaher, & Findling, 2008), conditions classified as BD differ among studies. Whereas some research groups, for example, identify multiple phenotypes for mania in pediatric BD, ranging from a narrow phenotype marked by elation or grandiosity and clear episodicity to a broad phenotype (termed severe mood dysregulation or SMD) that lacks these features, other researchers do not make this distinction

(Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003). Second, studies vary in their conclusions about whether BD-associated impairments are state-dependent (i.e., present only during mood episodes) or reflective of enduring trait-like characteristics that influence cognition and behavior even when individuals are asymptomatic. Whereas early studies focused minimally on this distinction, most recent research details participants' mood states and medications at the time of research participation or compares medicated and unmedicated and/or euthymic and symptomatic subgroups. Third, effects and correlates of both acute BD symptoms and enduring illness-related deficits are likely to differ across development; studies vary, however, in the degree to which they consider the developmental context of the affected individual.

This review first outlines key social/emotional milestones and their neural foundations. It then turns to the literature regarding socio-emotional functioning in BD and, finally, examines behavioral and neural differences in socio-emotional processes between affected/high-risk and typically-developing populations. Consistent with earlier reviews (e.g., (Dickstein & Leibenluft, 2006), this article focuses on recent findings regarding affective cue processing and flexible response generation and inhibition, both of which constitute promising candidate endophenotypes for BD.

Typical Socio-emotional Development: Functional and Neural Changes

Across development, social success and emotional adjustment require effective evaluation of and response to complex and dynamic interpersonal and environmental demands. More specifically, individuals must accurately perceive and interpret social cues, respond flexibly and appropriately to those cues, and regulate their emotional reactions throughout (Crick & Dodge, 1994). In typical development, these skills emerge gradually, mediated by a core network of neural structures (Nelson, Leibenluft, McClure, & Pine, 2005) that mature between

infancy and adulthood (Gogtay et al., 2004). According to one recent model grounded in the neuroscience literature, this network consists of reciprocally interactive detection, affective, and cognitive-regulatory systems that the authors term “nodes” (Nelson, Leibenluft, McClure, & Pine, 2005).

Structures within the detection node play central roles in detecting and decoding socially and emotionally salient environmental features, such as affective facial expressions or more complex interpersonal cues. This node, which encompasses the superior temporal sulcus, fusiform face area, and inferior temporal and occipital cortices, appears to function in a rudimentary fashion as early as the first years of life (Halit, Csibra, Volein, & Johnson, 2004; Johnson et al., 2005). During this period, infants learn to detect and respond to adult cues, thus laying a foundation for more complex skills, including joint attention and the capacity for dyadic and triadic interactions (Carpenter, Nagell, & Tomasello, 1998). In the ensuing years, using the same neural structures, children build on this base to become adept at reading social and emotional cues such as facial expressions (McClure, 2000) and using these cues to theorize about others’ states of mind (Wellman, Lopez-Duran, LaBounty, & Hamilton, 2008).

Neural regions such as the amygdala and ventral striatum, which are engaged by reward or punishment cues, constitute the affective node. These structures, which appear to become functional as early as the neonatal period (Bauman, Lavenex, Mason, Capitanio, & Amaral, 2004; Goursaud & Bachevalier, 2007) and to evolve through puberty (Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997; Nelson, Leibenluft, McClure, & Pine, 2005), evaluate stimuli for emotional salience and inform selection or inhibition of behavioral responses. Working in concert with structures in the cognitive-regulatory node (several regions within the

frontal cortices), the affective node mediates increasingly sophisticated and flexible responses to social and emotional demands in the environment.

Unlike structures in the detection and affective nodes, the cognitive-regulatory node remains functionally immature until adolescence and early adulthood (Gogtay et al., 2004). Via reciprocal projections that gradually come on-line, cognitive-regulatory structures modulate activity in and receive feedback from the other nodes (Barbas, 2007), contributing to increasingly sophisticated theory of mind processes, inhibition of prepotent responses, and generation of goal-directed behavior (Nelson, Leibenluft, McClure, & Pine, 2005). These skills emerge and evolve through middle childhood, when mechanisms for managing stress responses (Kliewer, Fearnow, & Miller, 1996), conforming to social rules for displaying emotion (Jones, Abbey, & Cumberland, 1998), and understanding others' mental states (Schwanenflugel, Fabricius, & Alexander, 1994) become more complex. These mechanisms, which are critical to successful interpersonal functioning, continue to develop well into adulthood (Fullerton & Ursano, 1994).

A growing body of evidence suggests that the maturation and interaction of the three nodes deviate from normal patterns in individuals with BD. This deviation may vary, however, depending on the age of disorder onset (e.g., pediatric versus adult), complicating the comparison of affected individuals of different ages. Individuals with early-onset BD, for instance, could experience atypical development within the early-maturing detection node that, in turn, sets off a cascade of effects on functioning in later-maturing brain regions. Individuals with later BD onset, in contrast, might experience a different pattern of functional neural anomalies. Research articulating the developmental course of BD would thus benefit from consideration of both neural and behavioral levels and their interaction. Further, such research

needs to extend to asymptomatic individuals at high risk for the disorder, who may show latent atypical patterns of neural development.

Socio-emotional Dysfunction and Neural Correlates in BD versus Typical Development

Clinicians and researchers widely recognize that individuals with BD, both adults and youths, show evidence of broad socio-emotional dysfunction (Cannon et al., 1997; Fagiolini et al., 2005; Geller et al., 2000; Pope, Dudley, & Scott, 2007; Reichart et al., 2007; Robertson, Kutcher, Bird, & Grasswick, 2001; Schenkel, West, Harral, Patel, & Pavuluri, 2008; Simon, Bauer, Ludman, Operskalski, & Unutzer, 2007). Indeed, taken as a whole, research findings suggest that after the initial onset of the disorder, most affected individuals experience at least some global socio-emotional impairment, both during active mood episodes and periods of euthymia. Research attention has thus shifted to more precise description of socio-emotional deficits associated with the disorder. Although studies have examined multiple putative areas of deficiency, the next section of the present article focuses exclusively on work comparing perception and interpretation of social/emotional cues and flexible formulation of responses to those cues in individuals with and without BD. This section also examines recent studies aimed at elucidating the neural underpinnings of these deficits in individuals with BD. A growing body of research has yielded evidence that both adults and youths with BD show atypically elevated activity in structures within the affective and detection nodes (e.g., the amygdala and related subcortical structures) along with abnormally muted activity in prefrontal regions within the cognitive-regulatory node (Bearden, Hoffman, & Cannon, 2001; Phillips & Vieta, 2007).

Perception and interpretation of socio-emotional cues

In both adults and adolescents with BD, findings from behavioral studies indicate the presence of fairly consistent global deficits in performance relative to typically developing peers

on tasks involving recognition and interpretation of emotionally-valenced social cues, such as facial expressions (Getz, Shear, & Strakowski, 2003; Amanda E. Guyer et al., 2007; Lembke & Ketter, 2002; McClure, Pope, Hoberman, Pine, & Leibenluft, 2003; McClure et al., 2005; Rich, Grimley et al., 2008; Schenkel, Pavuluri, Herbener, Harral, & Sweeney, 2007). Most studies have used forced choice emotion labeling tasks that require participants to select one of several labels for a stimulus face. A few more recent studies, however, have examined other aspects of facial expression processing or have tapped more complex social emotion processing skills.

In the largest facial emotion labeling study to date, Guyer and colleagues (2007) compared performance among diagnosis-free adolescents and peers with either BD, severe mood dysregulation (SMD; (Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003), anxiety or major depressive disorders, or ADHD/Conduct Disorder. Relative to controls and members of other clinical groups, participants in the BD and SMD groups showed global facial expression labeling deficits on a task that involved naming the emotions displayed in expressive photographs of adults and children. Although numerous participants in the BD and SMD groups, unlike those in other groups, were medicated, post hoc analyses indicated that group differences did not stem from this characteristic. Further post hoc analyses comparing euthymic participants with BD and controls yielded evidence of impairment in the euthymic BD group, suggesting that the deficits observed in the combined euthymic/symptomatic BD group were not mood state related.

Schenkel and colleagues (2007a) focused more explicitly on associations between facial expression processing deficits and both medication and current mood state in youths with BD (Schenkel, Pavuluri, Herbener, Harral, & Sweeney, 2007). In their study, three groups of young adolescents (diagnosis-free; diagnosed with BD, euthymic, and medicated with risperidone and either lithium or divalproex; or diagnosed with BD, acutely symptomatic, and unmedicated)

completed two facial expression processing tasks. On the first task, participants differentiated between two faces showing the same emotion at different intensities; on the second task, participants rated emotional expressions along a seven-point continuum ranging from very happy to neutral to very sad. Symptomatic/unmedicated youths with BD performed more poorly than controls or euthymic peers when differentiating between expressions of different intensities; both medicated and unmedicated youths with BD underestimated the intensity of emotional faces relative to diagnosis-free peers. These findings suggest different kinds of facial expression processing deficits may relate in different ways to BD; in particular, whereas impairment on discrimination task may be associated with acute symptomatology, impaired judgment of intensity may represent a trait or risk marker. Alternatively, differences in task difficulty may have led to different patterns of performance between symptomatic and euthymic/medicated youths with BD.

The prior two studies used static visual images as stimuli; a third recent study used a more nuanced and ecologically valid task to evaluate facial expression identification skill in youths with BD, SMD, or no diagnosis (Rich, Grimley et al., 2008). During each trial of this task, a neutral face was morphed gradually until it displayed an intense emotional expression (happy, surprised, sad, angry, fearful, or disgusted). Participants watched the morphing process for each item and pressed a button as soon as they could accurately identify the depicted expression. For all six emotions, youths with BD and SMD took longer than controls to respond; this suggests that they had more difficulty discerning subtle emotion signals. Further, although they were generally as accurate as controls in the labels they selected, youths in the patient groups required more emotional information before they could correctly identify disgusted, surprised, happy, and fearful faces. Interestingly, for participating BD and SMD patients, task

performance correlated significantly with scores on parent-report measures of social functioning, such that the less socially adept a participant was, the more intense the stimulus expressions needed to be for the participant to identify them accurately.

The three studies described above, like most of the earlier research, each focused on older children and adolescents with BD diagnoses. Almost no studies, in contrast, have been published examining preschoolers or youths who are at risk for BD by virtue of family history. One recent exception, however, provides preliminary evidence that impairment in particular aspects of emotion processing may be related to risk for BD, as well as active symptoms. Brotman and colleagues (2008) compared performance on the facial expression labeling task used in Guyer et al. (2007) between 4 to 18 year olds without BD diagnoses, but with an affected parent or sibling, and low risk controls. Results indicated that, like children and adolescents diagnosed with BD, the youths at high risk for BD showed globally deficient performance on the task (Brotman et al., 2008).

Thus, consistent with findings in adults (Getz, Shear, & Strakowski, 2003; Lembke & Ketter, 2002), youths with BD, as well as those at risk for the disorder, perform atypically poorly on tasks involving different kinds of facial expression processing (e.g., discrimination, labeling, evaluation of intensity). Patterns of performance vary, however, with the nature of the task and although deficits on some task types (facial expression labeling, evaluating intensity of an emotional expression) are apparent regardless of current mood state and thus may represent endophenotypes for the disorder, deficits on other tasks (e.g., discrimination between expressions of different intensities) appear more specifically related to the presence of active symptoms.

In addition to facial expression processing, researchers have found evidence of deficits on more complex socio-emotional cue processing measures, involving such skills as theory of mind

and social inference, in adults and adolescents with BD (Kerr, Dunbar, & Bentall, 2003; Schenkel, Marlow-O'Connor, Moss, Sweeney, & Pavuluri, 2008). Studies focused on adults with BD have found their performance to be impaired relative to controls on varied theory of mind tasks; deficits have been found in both symptomatic individuals (Kerr, Dunbar, & Bentall, 2003) and, in some studies, euthymic patients with BD (Bora et al., 2005; Pollak & Tolley-Schell, 2003). In the one published study to date focused on adolescents, Schenkel and colleagues (2008) also found group differences between those with BD and controls. In this study, the authors examined performance on two theory of mind tasks—one designed to measure ability to infer others' intents and the other developed to tap false-belief understanding in emotional contexts. Adolescents with BD performed significantly more poorly than diagnosis-free peers on both measures (Schenkel, Marlow-O'Connor, Moss, Sweeney, & Pavuluri, 2008).

Taken together, research findings in both adults and adolescents with BD are consistent with the presence of behavioral socio-emotional cue processing deficits. Whether these deficits are trait- or state-based remains unclear. However, results from a small number of studies provide compelling evidence that at least some skills within the socio-emotional processing domain are impaired in affected individuals regardless of current mood state. To more conclusively address this issue, research is needed that focuses on facial expression and other social cue processing in younger children with BD and more studies need to examine individuals who are at risk for the disorder.

A growing body of research that may help elucidate the nature of socio-emotional cue processing deficits in individuals with BD approaches the issue from a neuroscience perspective. In light of evidence that impairment in aspects of socio-emotional cue processing represents an endophenotype for BD, the recent spate of studies with a focus on neural correlates of these

skills, particularly facial expression processing, in BD is not surprising. In these studies, researchers typically use functional MRI (fMRI) to examine patterns of neural activation associated with varied responses to socio-emotional stimuli such as emotional faces.

Research on neural correlates of facial expression processing in adults with BD has yielded a fairly consistent pattern of increased activation in the amygdala and other subcortical regions and decreased prefrontal activation relative to controls. These group differences have emerged in studies that used a variety of facial expression processing tasks and that have compared diagnosis-free controls and both actively manic patients with BD (e.g., (Altshuler et al., 2005) and individuals with medication-stabilized BD in varying current mood states (e.g., (Yurgelun-Todd et al., 2000).

Not all studies, however, have yielded results that conform to this pattern, likely because of the marked variability in participant characteristics (e.g., current mood state or medication status), tasks (e.g., passive viewing of faces, expression labeling or rating, etc.), and facial expressions displayed (happy, angry, neutral, fearful, etc.). In one study, for instance, passive viewing of emotional faces elicited elevated activity both in subcortical structures and in prefrontal regions in euthymic and depressed adults with BD, relative to both controls and patients with major depressive disorder (MDD) (Lawrence et al., 2004). Another study, which required participants to rate the intensity of sad faces, found decreased amygdala and subgenual cingulate cortex and increased posterior cingulate cortex and posterior insula activation in manic patients with BD relative to diagnosis-free controls (Lennox, Jacob, Calder, Lupson, & Bullmore, 2004). In one of the few studies to compare performance across tasks and stimulus types, Chen and colleagues (2006) found that both currently manic and currently depressed adults with BD showed atypical patterns of activation relative to diagnosis-free controls.

However, different tasks and stimulus expressions elicited abnormal neural responses in the two patient groups (Chen et al., 2006). Neural responses to facial expressions in euthymic adults with BD have received limited research attention; however, one study found elevated hippocampal activation to fearful faces in euthymic adults with BD (Malhi et al., 2007).

Thus, although findings in adults with BD regarding directions of activation anomalies are mixed, the literature broadly indicates a pattern of atypical subcortical, most commonly amygdala, activation in concert with anomalous prefrontal activation. More recently, researchers have begun to examine the ways in which prefrontal and subcortical systems interact in both clinical and healthy samples during facial expression viewing tasks (A. E. Guyer et al., 2008; Keightley et al., 2003; Monk et al., 2008), which could help explain divergent findings among studies. This line of research is still relatively new and thus less comprehensive; however, at least one study of manic adults with BD has found a reduction in prefrontal regulation of the amygdala during expression labeling (Foland et al., 2008).

A second emerging line of research suggests that medication may normalize these atypical patterns of neural function. Patients with BD who were treated with lamotrigine, for example, showed changes in their patterns of activation during a facial expression recognition task, such that their brain activity more closely resembled that of healthy controls after treatment (Haldane et al., 2008; Jogia, Haldane, Cobb, Kumari, & Frangou, 2008). Other medications appear to have similar effects; Blumberg and colleagues (2005) found comparable changes in activation patterns in seventeen adults with BD following treatment with a range of medications (H. Blumberg et al., 2005). Much more research of this type is needed, however, as a recent review suggests that it may be premature to draw conclusions about medication effects on neural function (Keedwell et al., 2008).

Findings regarding neural correlates of facial expression processing in youths with BD are similar to those obtained in research on adults. Specifically, researchers have consistently found atypical activity to emotional faces in subcortical limbic regions and prefrontal structures. Studies conducted prior to 2006 have been comprehensively reviewed in previous publications (Dickstein & Leibenluft, 2006); the present article therefore focuses on work that has been published more recently. Although the field has advanced substantially since the earliest research was published, it is important to note that it remains limited in several respects. First, participants have consisted exclusively of older children and adolescents. Almost no neuroimaging studies have examined children under seven or eight years of age, in part because younger children are more likely to be distressed by MRI scans and less able, on average, to lie still in the MRI scanner for the duration of a task. Second, because of the difficulties inherent in recruiting carefully diagnosed youths with BD and successfully gathering MRI data, studies tend to combine participants across a broad age range—in many studies, participants aged eight to eighteen are combined in a single group. Potential age and pubertal status effects are thus likely to be obscured, particularly because few studies have included large enough samples to permit stratification along these variables. Third, as in the adult literature, participants vary across studies in terms of current mood state and medication status; further, facial expression processing tasks and target facial expressions have differed from study to study. These methodological differences render direct comparisons of findings across studies difficult.

Recent findings regarding adolescents' neural responses to emotionally expressive faces have been mixed, likely reflecting both task and sample differences. In one study, Pavuluri and colleagues (2007) instructed euthymic unmedicated adolescents with BD and diagnosis-free peers to passively view emotionally expressive (happy, angry, neutral) faces while undergoing

MRI scans. Participants with BD differed in patterns of activation from psychiatrically healthy peers; group differences varied, however, depending on the stimuli presented. Specifically, the BD group, showed reduced activation to angry and happy faces in the occipital cortex and in orbitofrontal and dorsolateral prefrontal regions. In response to happy faces alone, however, the BD group showed decreased medial prefrontal activation combined with elevated activity in the right amygdala and bilateral pregenual anterior cingulate cortex (Pavuluri, O'Connor, Harral, & Sweeney, 2007).

In a study that combined participants with active BD symptoms, either manic or depressed, with euthymic participants, neural anomalies emerged that were both similar to and different from those seen in Pavuluri et al.'s (2007) purely euthymic sample. In this study, Dickstein and colleagues (2007) instructed a mixed sample of adolescents with BD and a sample of diagnosis-free controls to rate different characteristics of emotional faces that they then had to identify during a surprise recognition task (Dickstein, Rich et al., 2007). In response to happy faces that they recognized later, participants with BD showed increased neural activation relative to controls in the striatum and anterior cingulate cortex. Successfully encoded angry faces, in contrast, elicited increased activation in the orbitofrontal cortex in the BD group. The degree to which differences from Pavuluri et al.'s (2007) findings reflect sample or task variations is unclear; research is needed that replicates each task in BD samples that differ according to mood and medication status.

Participants' idiosyncratic perceptions of facial emotion cues also need to be taken into account. Rich et al. (2006) examined patterns of activation while youths with BD (mixed sample of euthymic, depressed, and hypomanic participants) and controls rated the hostility conveyed by ostensibly neutral as well as their own fear levels during viewing of the faces (Rich et al., 2006).

The BD group showed elevated activation relative to controls in the left amygdala, accumbens, putamen, and ventral prefrontal cortex during hostility ratings and greater left amygdala and bilateral accumbens activation when rating their own fear. Notably, however, participants with BD rated neutral faces as more hostile and reported more fear when viewing them than did controls, raising the possibility that activation differences in the BD group were a function of biased perceptions rather than of responses to inherent stimulus characteristics.

Recent trends observed in the adult literature, including a shift toward studies of connectivity or interaction among brain regions and of treatment effects, are also evident in the adolescent literature. Rich and colleagues (2008), for example, examined group differences in correlations in patterns of activation between the left amygdala and other neural structures during a task that required participants to rate both emotional and nonemotional aspects of expressive faces. Consistent with Foland et al.'s (2008) findings in adults, results showed less functional connectivity between the left amygdala and both the right posterior/precuneus region and the right fusiform/parahippocampal gyri, in youths with BD than in controls (Rich, Fromm et al., 2008).

At the time of this review, no published studies in adolescent samples had examined treatment responses to emotional faces. One study, however, that used emotionally valenced scenes as stimuli (Eaton et al., 2008) yielded preliminary evidence of comparable treatment effects to those observed in adults. In this study, a small sample ($n=8$) of adolescents with BD who were currently in depressive episodes received lamotrigine for eight weeks, with fMRI scans during viewing of positive and negative scenes completed before and after treatment. After the completion of treatment, amygdala activation in response to negative images declined from pre-treatment levels; notably, magnitude of activation decrease was significantly correlated with

clinical improvement. Given the small sample size and the lack of a control group, these findings are, as the authors point out, necessarily preliminary and will need replication in larger controlled samples. However, this study constitutes an important first step toward extending adult findings regarding neural effects of successful treatment to younger individuals with BD.

Findings in both the adult and adolescent literatures on neural correlates of facial expression processing in BD thus provide compelling evidence that atypical interactions between subcortical—primarily limbic—and prefrontal systems in response to facial emotion characterize individuals with the disorder. Specific anomalies vary across studies, depending on sample composition, task administered, and stimulus characteristics, but research is largely consistent in finding differences in patterns of neural activity in prefrontal and limbic regions between patients with BD and typically developing individuals. Further, findings suggest that neural anomalies are present in euthymic as well as actively manic and depressed individuals. Notably, however, successful treatment may diminish at least some of these differences.

Research on facial expression and other social cue processing in BD, as well as their neural correlates, has increased markedly in recent years. A large number of questions, however, remain to be addressed in this area. First, research that directly compares adult and adolescent samples with BD is needed. Without such direct comparison, the degree to which differences in both behavioral and neural responses from healthy individuals are consistent across development will remain unclear. Inclusion of larger numbers of pre-adolescents will also be useful in future studies, as it will permit examination of the effects of as yet unstudied variables such as age and pubertal status. Second, further cross-sectional research that compares separate samples of manic/depressed/euthymic or medicated/unmedicated participants or, if possible, within-participant longitudinal research with scans obtained during different mood episodes is needed to

elucidate effects of mood state and medication. Third, standardization of tasks across studies, such that different samples complete the same behavioral tasks, will be useful in further clarifying the sources of variability within the literature. Finally, extension of this research literature to individuals who are at risk for BD, but do not meet diagnostic criteria, will help in identifying state-related versus trait deficits or differences.

Cognitive and Behavioral Flexibility

In day to day interactions, individuals must not only accurately perceive and respond to socio-emotional cues, but they must also perform these tasks in ways that are adapted to constantly evolving environmental demands. This requires the combination of cognitive and behavioral flexibility with effective regulation of one's own emotional reactions. These higher order processes are particularly critical when interactions or circumstances do not proceed in expected ways and evoke intense affect.

Researchers have typically measured cognitive flexibility in individuals with BD using neuropsychological tasks designed to measure aspects of executive functioning, such as the ability to shift attention in response to contingency cues. Such tasks include the classic Trails B measure and Wisconsin Card Sorting Task, as well as the intra-extra dimensional shift task (IED shift task; (Robbins et al., 1998)) Recent studies have also used the Change Task (Logan, Schachar, & Tannock, 1997), which measures the ability to inhibit a pre-potent response and substitute an alternate one and permits adjustment of task difficulty to ensure that participants execute correct responses approximately 50% of the time on trials requiring response substitution.

A number of behavioral studies have examined cognitive flexibility and emotional regulation in adults with BD as compared to typically-functioning adults. Findings consistently

suggest, the presence of deficits that, in some samples, persist at subtle levels even when mood is stable (Fleck et al., 2003; Martinez-Aran et al., 2004; Mur, Portella, Martínez-Arán, Pifarré, & Vieta, 2007). Martinez-Aran and colleagues (2004), for instance, found evidence of deficits on tasks such as the Wisconsin Card Sorting Task (WCST) and the Stroop Color-Word Test, both of which require cognitive flexibility, in both acutely symptomatic and euthymic participants with BD. Findings from a more recent study, however, suggest a more nuanced pattern of group differences. Fleck and colleagues (2008) found that individuals in manic or mixed BD episodes performed more poorly than controls on the WCST. However, chronicity of disorder appeared to influence effects. Specifically, euthymic individuals with BD showed better performance than symptomatic individuals who had experienced multiple episodes. They did not, however, differ significantly in performance from symptomatic patients in their first mood episode.

In adolescent samples, research has revealed similar evidence of differences between individuals with and without BD. Dickstein and colleagues (2007), for example, administered the IED shift task and the Change task to youths with BD, SMD, and controls. Relative to controls and peers with SMD, adolescents with BD were impaired on simple reversal learning trials during the IED shift task. On the change task, members of the BD group also showed impairment relative to adolescents with SMD on trials that involved substituting novel responses for prepotent responses. These deficits remained significant even when current mood state, comorbid anxiety, and comorbid ADHD were accounted for (Dickstein, Nelson et al., 2007).

Meyer and colleagues (2004) administered the WCST and Trails B tasks to offspring of mothers with mood disorders (unipolar or bipolar) or no history of psychiatric illness in the context of a prospective longitudinal study of risk for affective disorders. Offspring completed the WCST and Trails B during adolescence and were subsequently followed into adulthood,

when they were evaluated for BD. High rates of impairment on the WCST were evident in offspring of mothers with BD who later developed BD themselves (19%); in particular, they made atypically frequent perseverative errors and gave abnormally few conceptual level responses. These findings of impaired performance in only the subset of high risk individuals who went on to develop BD provide suggestive evidence that cognitive flexibility deficits may represent a risk marker for the disorder (Meyer et al., 2004). Findings from a follow-up study of the same sample, however, indicate that the associations between cognitive inflexibility and risk for BD are more complex. In this study, Meyer et al. (2006) found WCST performance to be a mediator of associations between maternal negativity when their offspring were toddlers and later development of offspring BD (Meyer et al., 2006). Taken together, these two studies suggest that genetic risk, parent behavior, child cognition, and child outcome interact dynamically over time to influence outcomes. Clearly more such longitudinal work that examines reciprocal influences among these and other relevant variables is needed to follow up on these interesting results.

Most studies to date regarding cognitive flexibility and regulation have used affectively neutral cognitive tasks. One recent study of youths with BD, however, focused on regulation of emotional, cognitive, and behavioral responses to changing contingencies (Rich et al., 2007). Children and adolescents with BD, SMD, or no diagnosis completed the Affective Posner task, which assesses attention under a variety of emotional circumstances and contingencies. Of particular interest with regard to BD is a frustration condition, in which participants win or lose money based on a rigged algorithm that caused them to lose money regardless of their accuracy or speed. Youths with BD or SMD reported significantly more arousal during the frustration

condition than controls, which suggested difficulty regulating their emotional responses to unpredictable contingencies.

Research on neural responses during tasks requiring cognitive flexibility and response inhibition in adults and adolescents with BD has typically used different tasks than those employed in the behavioral literature, including modifications of the classic Stroop and go/no-go tasks, which require selective attention, inhibition of pre-potent responses, and effortful substitution of alternate responses. Findings consistently indicate atypical activation in prefrontal and subcortical networks that include limbic and striatal structures, although patterns of anomaly differ depending on the samples under study.

Several studies that included samples of adults with BD who were euthymic (Kronhaus et al., 2006; Lagopoulos & Malhi, 2007; Malhi, Lagopoulos, Sachdev, Ivanovski, & Shnier, 2005) or in varied mood states (Roth et al., 2006; Yurgelun-Todd et al., 2000) found differences from controls in patterns of activation during both emotional and non-emotional variants of the Stroop task. In most of these studies, BD patients showed decreased prefrontal activation relative to controls. Although localization of reduced activation within prefrontal regions varied among studies, findings of attenuated activity in ventral and medial prefrontal regions were common.

Deviations from this pattern of findings were also common, possibly reflecting task variations or sample differences. One study, for example, found evidence of *increased* dorsolateral prefrontal activation and decreased anterior cingulate activity, in adults with BD versus controls (Yurgelun-Todd et al., 2000). Two other studies, each of which compared depressed adults with BD to controls during performance of a Stroop measure, found no evidence of group differences in activation in frontal regions (Marchand, Lee, Thatcher, Jensen et al., 2007; Marchand, Lee, Thatcher, Thatcher et al., 2007).

Like the research using Stroop task variants, studies that have administered go/no-go task variants have yielded inconsistent findings across participants in different mood states. Wessa and colleagues (2007), for example, gathered data regarding neural activity during emotional versus nonemotional go/no-go tasks. In this study, activation in the orbitofrontal cortex, temporal regions, insula, and both anterior and posterior cingulate cortices was increased in euthymic adults with BD relative to diagnosis-free controls (Wessa et al., 2007). Altshuler and colleagues (2005), on the other hand, found decreased right orbitofrontal cortex, hippocampus, and left cingulate cortex activation in manic adults with BD during a non-emotional go/no-go variant. These inconsistencies between studies point to a need for research that compares performance on identical tasks in samples that differ according to mood state. Ideally, studies will also directly compare patterns of activation in response to emotional and non-emotional stimuli within go/no-go tasks, as some evidence suggests that emotionally valenced stimuli elicit distinctive patterns of neural engagement (Shafritz, Collins, & Blumberg, 2006).

In adolescents with BD, as in adults, neurally-focused research has largely used Stroop and go/no-go tasks. Despite this consistency in methodology, patterns of group differences in activation have not overlapped uniformly between studies of youths and adults. For example, although Blumberg and colleagues (2003) replicated adult findings of increased ventral prefrontal cortical activation in depressed and euthymic adolescents with BD during a color-naming Stroop task (H. P. Blumberg, Leung et al., 2003), they obtained a different pattern of findings in manic adolescents and in participants in a second study. The second study yielded no evidence of group differences in prefrontal activation between adolescents with BD relative to controls during a color-naming Stroop task, although the BD group showed subcortical (putamen and thalamus) hyperactivity (H. P. Blumberg, Martin et al., 2003). These mixed findings

underscore the importance of considering the role of developmental factors in patterns of emergence of neural anomalies, particularly in prefrontal regions, which continue to mature during adolescence and into early adulthood (Gogtay et al., 2004).

Two recent neuroimaging studies focused on adolescents with and without BD used the stop signal task, a go/no-go task variant that permits separate examination of successful and unsuccessful response inhibitions and substitutions, as a measure of cognitive flexibility and inhibition (Leibenluft et al., 2007; Nelson et al., 2007). Nelson et al. (2007) found that in the context of comparable task performance, participants with BD showed more activation in the dorsolateral prefrontal cortex and primary motor cortex than did matched controls on trials when they successfully substituted effortful responses for pre-potent responses. Leibenluft et al. (2007), in contrast, examined trials on which participants failed to correctly inhibit responses. Results were consistent with attenuated striatal and right ventral prefrontal cortex activation in BD patients compared to controls on these trials.

Taken together, the adolescent and adult literatures suggest that BD is associated with impaired cognitive flexibility and regulation across development. Further, although specific findings vary across studies and age groups, they are broadly consistent in their implication of fronto-striatal dysfunction as the neural substrate of this cognitive and behavioral impairment. More research is needed comparing patterns of behavior and neural activity across age groups, however, because as Blumberg and colleagues (2004) pointed out the manifestations of BD may vary depending on the timing of disorder onset due to variability in the maturation rates of different structures within fronto-striatal circuits. Thus, disorder onset during early adolescence, which would coincide with one stage of frontal cortical development, may differently affect both

neural activity and behavior than does disorder onset in early adulthood, which coincides with a later stage (H. P. Blumberg et al., 2004).

Conclusions and Future Directions

Despite an array of subtle inconsistencies in the literature, findings generally converge to indicate that individuals with BD, regardless of the timing of their symptom onset, show neurally-mediated socio-emotional deficits. Atypical patterns of emotional cue--particularly facial expression--processing, as well as cognitive and behavioral inflexibility, have been identified fairly consistently in both euthymic individuals with BD and those at risk for the disorder. As a consequence, both hold promise as potential endophenotypes for the disorder, mediated by functional anomalies in fronto-limbic neural circuits. A number of questions, however, remain to be answered if we are to understand and address the impact of BD on socio-emotional functioning and its neural correlates.

First, most published research focuses on individuals who are currently in mood episodes or in remission from such episodes rather than those at risk for BD. Prospective study of high risk groups is necessary if researchers are to identify risk and prodromal markers that might inform prevention and early treatment efforts. Gogtay and colleagues (2007) took an important step in this direction in a recent longitudinal study that examined brain structure in high-risk youth, approximately a quarter of whom were eventually diagnosed with mania. The children who participated in this study each exhibited multiple impairments, which typically included emotional and attentional dysregulation; unimpaired controls were also recruited. Each participant received multiple structural MRI scans over a four to eight year period, permitting the authors to examine neural changes over time. In the subsample (n=9) who met criteria for mania during the study, as well as in the non-manic impaired youths,,results indicated subtle differences

from controls in terms of change over time. Specifically, the impaired groups showed bilateral decreases in anterior cingulate regions and increases in left temporal structures over time, relative to their unimpaired peers (Gogtay et al., 2007). Replication and extension of such work, as well as comparable longitudinal research on functional aspects of the brain, should advance knowledge about BD, its antecedents, and markers of risk.

Additionally, further research on youths at risk for BD because of family history is critically needed. Ideally, studies will follow high-risk individuals from gestation or infancy, facilitating the identification of neurodevelopmental characteristics associated with later emergence of symptoms. Research on neural function in infants and young children is almost non-existent, given that current imaging techniques require participants to lie still and to attend to repetitive tasks for longer periods of time than is feasible for many preschoolers. Further, many behavioral tasks that are used in adult and adolescent samples are too difficult for young children to complete. However, advances in imaging technology and creative adaptation of tasks may increase the probability that studies of neural activity in individuals at risk for BD can be extended to younger age groups.

Finally, research needs to take into account the impact of development on the socio-emotional correlates of BD. Studies to date have yielded a number of mixed findings regarding both neural and behavioral concomitants of both actively symptomatic and remitted BD, particularly in child and adolescent samples. These inconsistencies likely stem, at least in part, from the practice of combining youths of widely varying ages in single samples, which could obscure important age or pubertal status effects. It is exceedingly difficult to recruit clinical samples large enough for examination of such effects, particularly in the context of neuroimaging research, in which data loss due to movement, inability to tolerate the scanning

environment, or other factors is common. Studies that pool participants' data from multiple sites provide one means of addressing this problem; for studies of neural function, however, between-scanner variability complicates such data pooling and replication of research in different age groups may be more feasible.

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