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Elucidating neural network functional connectivity abnormalities in bipolar disorder: toward a harmonized methodological approach

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Abstract

Bipolar disorder (BD), a mood disorder characterized by emotional lability and dysregulation, is associated with alterations in functional connectivity, particularly as assessed using functional MRI. Here, we provide an overview of the extant literature, and themes that have emerged within it. We identified published research describing functional connectivity in BD using PubMed and follow-up searches. The most consistent evidence favors abnormally heightened functional connectivity between the amygdala and the lateral regions of the ventral prefrontal cortex (PFC), both during rest or emotional processing. Altered interactions between the amygdala and more medial PFC regions have been implicated in BD, but are less consistently related to core symptoms and are sometimes associated with mood state or psychosis. Interactions between medial and lateral ventral PFC have also been reported to be altered in BD, and may mediate estimates of amygdala/vlPFC connectivity. We also describe other themes, including an emerging literature examining reward circuitry, which has highlighted abnormal functional interactions between the ventral striatum and medial prefrontal cortex, as well as the advent of examining global network abnormalities in BD. Functional connectivity studies in BD have established altered interactions between PFC and the amygdala. To address the inconsistencies in the literature, we suggest avenues for the adoption of large scale, and network-based analysis of connectivity, the integration of structural connectivity and the acknowledgement of dynamic and context-related shifts in functional connectivity as a means of clarifying the abnormal neural circuitry in the disorder.

Keywords

Bipolar disorder; depression; functional connectivity; amygdala; prefrontal cortex; global networks

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INTRODUCTION

The rapid development in recent years of increasingly more sophisticated techniques for examination of neural network functional connectivity (1) has motivated their employment toward the study of neural networks of interest in a variety of different psychiatric disorders, including bipolar disorder (BD). The advantages of utilizing these techniques are multiple, including the ability, alongside the use of more conventional regional BOLD signal (activation) analyses, to elucidate functional relationships among specific neural regions and networks of interest, providing a more nuanced understanding of abnormalities in neural network dynamics. The use of such techniques can thereby help identify an additional array of disorder (or behavior)-specific neural biomarkers, that reflect measures of functional coupling between neural regions and networks, and can provide additional targets for existing and novel interventions. In bipolar disorder, the majority of neuroimaging studies have focused on examination of emotion processing and emotion regulation neural circuitries (2-4), and yet relatively few such studies have employed functional connectivity techniques. Those studies that did employ such techniques largely focused on localized networks, often comprising a small number of neural regions, informed by previous, activation-based neuroimaging studies of the disorders. The particular experimental focus on the interaction of subcortical regions such as the amygdala and striatum with the prefrontal cortex (PFC) has led to a dominance of functional MRI studies in the extant literature, in contrast to other methods such as EEG. The examination of global, largescale neural network connectivity in bipolar disorder has been more limited.

The focus of this critical review is thus threefold.

1. To review the present literature regarding findings from neuroimaging studies that employed functional connectivity techniques in BD, and the themes that have emerged to date.
2. To delineate strategies to move toward a rational, larger scale network approach to examining neural network functional connectivity in BD, without losing focus on the more circumscribed neural circuitries shown to be implicated in the disorder.
3. To outline the future directions that are needed in the study of neural network functional connectivity to enable significant advances to be made in understanding the neural mechanisms of BD, and related, disorders.

FINDINGS FROM FUNCTIONAL CONNECTIVITY STUDIES IN BIPOLAR DISORDER

Localized network approaches

Much of the work examining functional connectivity in BD to date has focused on pairwise interactions between regions, sometimes as part of a wider neural network. Functional connectivity metrics generally rest on the assumption that the statistical association between activation of two regions (e.g. correlation) indicates the transfer of information between them. This statistical association can be estimated from activation data obtained during the

resting state (5), or via modelling task or context-related changes in functional connectivity via psychophysiological interactions (PPI: (6)) or dynamic causal models (DCM: (7)). These methods all require the specification of neural regions of interest, and have often included the following: amygdala, ventral and dorsal prefrontal cortices, and pregenual regions of the anterior disorder that emphasize, as a potential neural mechanism underlying emotional lability and mood dysregulation, abnormally increased activation in amygdala, implicated in emotion and salience perception, and decreased activity in prefrontal and anterior cingulate cortical regions, implicated in cognitive control processes (8-10). More recent neural models, that emphasize patterns of abnormally elevated activation in prefrontal cortical-striatal reward circuitry as a mechanism for reward sensitivity and impulsive sensation seeking in bipolar disorder (4), provide additional neural regions for use in localized network functional connectivity analyses. Accordingly, much of the investigation of functional connectivity in individuals with bipolar disorder has focused on these networks, often using emotional paradigms. Importantly, the amygdala shows widespread functional interactions with the prefrontal cortex, as reflected in underlying structural connectivity (11).

To provide an overview of the literature thus far, we identified fMRI studies examining functional connectivity in BD using searches of the PubMed database, employing search terms such as ‘bipolar disorder connectivity’, ‘bipolar connectivity fMRI’, ‘bipolar psychophysiological fMRI’, ‘bipolar resting fMRI’. Studies which examined a group of adult participants with BD and employed a measure of functional connectivity were compiled. From these studies, we selected those which focused on the neural circuitry of BD, as opposed to examining distinctions between different cohorts with predominantly psychotic symptoms, or discriminating different patient groups using machine learning algorithms. The first studies were published around 2009, and we continued our searches until October 2015.

Interactions between the lateral regions of the ventral prefrontal cortex and amygdala have been frequently shown to be altered in bipolar illness. These regions can include the most lateral regions of the ventral surface of the prefrontal cortex (i.e. ventrolateral PFC (vlPFC); BA47), the frontal operculum, as well as more centrally located regions of lateral orbitofrontal cortex (OFC). In a number of studies, connectivity between the amygdala and vlPFC was shown to be more positive in individuals with BD compared with healthy controls: these include task based studies (Table 1), as well as resting fMRI studies (Table 2). In the ‘Altered connections’ column of these tables, relevant connections are highlighted, and the direction of the effect briefly summarized. In all studies, aside from two exceptions described below, reporting differences in connectivity between the amygdala and vlPFC, all show either more positive or less negative connectivity than controls. The bias towards more positive connectivity is also present when healthy individuals show negative coupling: for example, Townsend and colleagues (12) observed weaker inverse (i.e. less negative) connectivity between the left vlPFC and the left amygdala in individuals with BD relative to healthy controls during emotion regulation. Intriguingly, a recent study of the offspring of individuals with bipolar disorder also revealed more positive connectivity between amygdala and left vlPFC compared to control cohorts, although selectively for happy faces (13). Altered connectivity in this circuit may therefore be a potential endophenotype of BD. However, two studies suggest the potential for other influences on

this connection. Dima and colleagues demonstrated using DCMs that the interactions between the amygdala and vIPFC could be influenced by different types of emotional stimuli in BD, but not in healthy controls (14). Similarly, Horacek and colleagues demonstrated differential modifications of amygdala-vIPFC connectivity in response to emotional faces and mood induction (15).

By contrast to the aforementioned studies of vIPFC-amygdala connectivity, Almeida and colleagues (16) observed reduced connectivity between the OFC and amygdala in individuals with BD relative to healthy controls in both hemispheres, and on the left relative to individuals with MDD. A potential explanation of the discrepancy between this study and those previously reviewed was that the OFC region of interest was medial. Indeed, the distinction between the functional connectivity of medial and lateral regions of the PFC may be of particular relevance for understanding neural mechanisms associated with BD. (For the purposes of this review, we will define medial prefrontal cortex (mPFC) as medial OFC and ventromedial PFC, as well as more dorsal regions such as the pregenual region of the anterior cingulate cortex (pgACC)). Functional connectivity between amygdala and more medial regions of the PFC has also been shown to be altered in individuals with BD during task performance (17, 18) and at rest (19, 20) in several studies, but without a clear direction of effect emerging (Tables 1 and 2). It is possible that the differential patterns of amygdala-vIPFC and amygdala-mPFC connectivities that are emerging in studies of BD may reflect specific functional abnormalities in lateral PFC-based voluntary/effortful emotion regulation and mPFC-based automatic/implicit emotion regulation pathways (10, 21). Findings suggest that the former pathway may be compromised by aberrant encoding of emotion in the amygdala, resulting in an inefficient, compensatory regulation of the amygdala by vIPFC, or by abnormally elevated signaling of emotion from amygdala to vIPFC. By contrast, the latter pathway may show a relative disconnectivity pattern, resulting in deficient amygdala regulation (Figure 1).

Interestingly, there is some evidence that, although an mPFC-amygdala pathway is often implicated in BD, it may be modulated by symptoms that are also characteristic of other psychiatric disorders, such as psychosis. For example, Anticevic and colleagues observed that connectivity in this pathway at rest was modulated (increased) by the presence of psychotic symptoms (22). Another relevant factor is the mood state of the individual. Of the studies we have compiled, a number examined the effect of different mood episode states upon functional connectivity by comparing patients in different phases of the illness. Several of these studies have identified differences in the mPFC-amygdala circuit across different mood states. For example, Anand and colleagues (24) showed that pgACC coupling with the left amygdala appeared to differ between manic and depressed individuals with BD. Perlman and colleagues using Granger Causality Mapping showed that amygdala connectivity with the prefrontal cortex, particularly in medial regions, differed between depressed and remitted individuals with BD (25). Versace and colleagues also demonstrated mood-state dependent differences between medial OFC and the right amygdala (26). However, they also demonstrated that interactions with the left amygdala were consistent across mood state, while Li and colleagues have also shown relatively consistent interactions between amygdala and posterior OFC across mood state (19).

In addition to evidence of alterations in PFC connections with the amygdala, there are also observations of altered connectivity between the vIPFC and mPFC, although the direction of the effect is not yet clear (27-30). Integrating the known connections between amygdala, mPFC and vIPFC/lateral OFC, Torrisi and colleagues (31) presented a mediational model of resting functional connectivity, in which the mPFC partially mediated the effect of amygdala activation on the vIPFC (see also (32)). This may be an important future direction, particularly if, as we have argued, the amygdala's connection with the mPFC is less specifically related to BD than its connection with the vIPFC. Using this type of approach, it may be possible to identify the extent to which the specific abnormality in the amygdala-vIPFC connection is partially determined by the mPFC (31), or even whether the abnormality is better understood in terms of more complex interactions between PFC regions (33). Notably, other prefrontal regions are sometimes implicated, including the dorsolateral PFC (dlPFC) and superior frontal gyrus (SFG). The dlPFC may also play a role in regulating the amygdala, and there is evidence for alterations of this pathway in BD (34-36). The SFG has been identified using seeds in other PFC regions (23, 37), and thus may reflect alteration within the PFC.

Recent studies have also demonstrated altered connectivity in reward-related networks, particularly the ventral striatum and its interactions with medial PFC regions (e.g. (38-40)). As with interactions between the amygdala and mPFC, interactions between the VS and mPFC can distinguish individuals with BD from healthy controls, but existing evidence does not strongly support specific alterations for BD over other mood disorders (38, 41). Nevertheless, focusing on reward processing has yielded evidence of specific neural characteristics of BD (4, 41-43), and it seems likely that functional connectivity will be a similarly productive area.

Specificity of altered connectivity for bipolar disorder

One question that is raised by our focus in BD on the main pairwise connections described above is the extent to which abnormalities in these connections are also observed in other psychiatric disorders. This information is crucial if connectivity measures are to be considered as biomarkers, and also informs the interpretation of the functional role of such connections. As with BD, a variety of analytical and theoretical approaches have been adopted when considering disorders such as major depressive disorder (MDD) and anxiety disorders, with findings indicating a wide variety of different functional connectivity patterns in these disorders. There are some consistencies with, and divergences from, the BD literature when considered in terms of the reductive model we propose above, however (Figure 1). For example, Anand and colleagues demonstrated reduced mPFC-amygdala connectivity at rest in individuals with BD, but also observed a similar pattern in individuals with MDD (24). Indeed, interactions between the amygdala and mPFC have been associated with anxiety (44) and mood disorders. Within a synthesis of the literature on MDD, Mulders and colleagues describe a neural model that specifies heightened connectivity between the anterior default mode network (DMN) – which includes the mPFC – and the amygdala (45). There are also demonstrations of abnormalities in this circuit in cocaine addiction (46). A further complicating factor is the influence of antidepressant medication on this network (47), given that it is often necessary to scan medicated patients (48). Thus, although the

specific nature of abnormalities in mPFC-amygdala connectivity may alter across different studies of BD, MDD, and anxiety disorders, the mPFC-amygdala connection has emerged as a key neural circuit of relevance to understanding neural mechanisms underlying this wide spectrum of psychiatric disorders.

Evidence for abnormalities in the other connections including the vIPFC, are somewhat less commonly reported. For example, Etkin and colleagues reported reduced amygdala-vIPFC connectivity in individuals with generalized anxiety disorder (GAD) (49), while Ramasubbu and colleagues (50) reported reduced left amygdala-vIPFC connectivity in individuals with MDD. In a study of individuals with PTSD, Brown and colleagues (51) also showed reduced interactions between amygdala and IFG (close to the vIPFC), but heightened connectivity between amygdala and a relatively dorsal mPFC region.

Together, these findings indicate that abnormalities are reported in amygdala-mPFC and amygdala-vIPFC neural circuits in psychiatric disorders other than BD. Consequently, future studies may benefit from adopting a trans-diagnostic dimensional approach (52), in which connectivity patterns could be related to particular symptoms, personality dimensions or mood state over and above metrics of general illness severity or medication load.

Link with basic neuroscience models of emotion regulation

Findings from translational studies can provide particularly significant insights into the type of neural functioning alterations that might underlie the above observations of aberrant functional connectivity in bipolar disorder. In particular, it is now well established that functioning of the amygdala and nucleus accumbens are contingent on the integrity of, and functional connectivity with, prefrontal regions. For example, Schoenbaum and colleagues have demonstrated that behaviorally relevant encoding in the amygdala is dependent on the integrity of the OFC (53), and vice versa (54). Likewise, encoding of behaviorally relevant cues in the ventral striatum has also been shown to be altered by OFC lesions (55).

A similar approach has been applied to the monkey frontal lobe: amygdala lesions were found to reduce but not eliminate value-related neural encoding in the OFC, while leaving similar encoding in the mPFC relatively unchanged (56). The extent of the alteration in the OFC provides some insight into the redundancy of neural circuitry required for OFC value encoding (56), which might inform more comprehensive models for human studies. Practically speaking, missing significant regions (and associated measurements) from the architecture of a proposed connectivity model has the potential to lead to significant model mis-estimation (57). Moreover, although the precise homology between human ventral prefrontal cortex and that of the monkey or rodent remains uncertain ((58) but see (59) for a somewhat compatible finding in humans), the dissociation observed by Rudebeck and colleagues is intriguing. Differentiation of function within the PFC on the basis of amygdala connectivity is conceptually similar to the distinct amygdala-VLPFC and amygdala-mPFC pathways we have discussed, but the particular relevance for BD remains to be established.

As well as direct interactions with the mPFC, the amygdala may also modulate the interactions of the mPFC and NAcc (60). This is potentially relevant in light of identification of modulated VS-mPFC interactions in BD described previously (e.g. (39, 40)), as well as

abnormal connectivity between amygdala and VS (19). Whether the amygdala is responsible for aberrant interactions between the VS and PFC observed in individuals with BD (as opposed to MDD, for example) remains to be examined fully.

GLOBAL NETWORK APPROACHES

By contrast with localized network methods, there are fewer applications of global connectivity methods to studying bipolar disorder (Supplement 1). These have included whole-brain ICA studies, in which the interactions or spatial extent of major large-scale networks have been investigated (35, 61, 62). Importantly, some of these studies revealed findings compatible with the data previously reviewed, including alterations in left vlPFC/opercular regions (61), reduced interactions between right dlPFC- and amygdala/striatum-related independent components (35), and heightened connectivity between medial and lateral PFC subregions (63). By replicating similar networks to seed based studies, such findings also provide important validation of previous work, given that they may be less susceptible to bias. These studies may also identify other, less strongly anticipated networks: Teng and colleagues (64) analyzed whole-brain correlations in terms of underlying modules, identifying patterns of pairwise alterations between regions, generally in DMN and striatal/thalamic circuits.

Attempts to examining functional connectivity in BD in terms of network-based statistics are few (see also (65) for analysis of structural connectivity in BD). In several of these studies, metrics describing patterns of network connectivity have been related to overall depression severity rather than other symptoms of BD. For example, Satttherthwaite and colleagues (38) examined network metrics of regions within reward-related networks in the mPFC, striatum and insula, finding nodal connectivity to be reduced with greater depression severity across MDD and depressed BD patients in the left ventral striatum. Compatible approaches have been applied to EEG data (66), several network metrics were altered in BD including weighted clustering and global efficiency, while certain network properties such as characteristic path length and small-worldness were found to be related to depression severity. He and colleagues (63) also found (albeit uncorrected) relationships between depression severity and nodal graph measures from several regions including the dlPFC and ACC. In addition, at a global level, they also showed increases in clustering coefficient, global efficiency, local efficiency and shorter characteristic path lengths in BD compared to MDD.

Possible integrative approaches to functional connectivity

Given that the two different approaches to examining functional connectivity, i.e., localized versus global network approaches, provide distinct frameworks to elucidate the nature of neural network functioning, it is worth considering how they may be synthesized to provide a more complete picture in BD. Most obviously, the global network-based approach generally specifies a greater range of connections, and thus the potential for mis-specifying a relationship by missing possible mediating interactions may be reduced. Incremental development of localized network models could be informed by global approaches, particularly if conducted on separate data.

Another important step has been the acknowledgement of dynamic shifts in the connectivity structure of the brain within the resting state (67), as well as the quantification of context, or task-related, changes in global network connectivity (e.g. (68)). Although the effects of task-related manipulations and spontaneous changes in connectivity during resting state may be different, the idea that functional connectivity can occupy different, context-dependent states is common to both.

The relationship between the structure and function of the connectome is an area of ongoing study (69). Structural studies of bipolar disorder have revealed focal abnormalities in grey matter density (70) as well as alterations in white matter structure (71). Inferring patterns of altered functional connectivity on the basis of structural connections would provide a framework for deriving more specific hypotheses and constraints over network models, and is supported by existing data (18, 26), and may be valuable for isolating distinct effects of abnormal structure as opposed to phenomena related to state/context, plasticity, compensation or neural inefficiency. In addition, a recent structural study provided important insights into the connectivity of subcortical regions such as the amygdala and striatum (72). Using structural connectivity estimates, the authors developed a metric (embeddedness) describing the interaction between given regions and other regions across different levels of brain hierarchy. Regions such as the amygdala were found to have relatively strong connections across many levels of the brain. This study raises the possibility that neural regions that are altered in BD are ones which may benefit from a somewhat different characterization within a network-based framework.

SUMMARY AND FUTURE DIRECTIONS

Functional connectivity studies have great potential to elucidate neural mechanisms of disorders such as BD. Yet, taken together, findings from localized and global neural network approaches indicate a variety of different patterns of abnormal functional connectivity in individuals with the disorder. Localized neural network approaches have focused predominantly on amygdala and striatal-prefrontal cortical networks during emotional processing, emotional regulation and cognitive control tasks. While several of these studies have shown, in individuals with BD, both abnormally increased positive functional connectivity between amygdala and vlPFC, or abnormally decreased inverse functional connectivity between these regions, there are also some discrepant findings potentially related to state/task related influences. Similar findings of enhanced connectivity have been observed using resting state fMRI. Connectivity between the amygdala and medial prefrontal regions has also been implicated in BD, but the direction of findings is less consistent and may be susceptible to a wide range of influences. Interactions within the prefrontal cortex, particularly between medial and lateral regions, have also been shown to be abnormal in BD, but the direction of effect is inconsistent. Global network approaches and ICA have not been applied widely, although in some cases have identified aberrant networks explored in localized studies.

The wide variety of different findings from these studies indicates the need for approaches that combine both localized and global network methodologies. Most obviously, the application of more sophisticated localized models describing the function of key nodes may

ensure that relevant modulatory phenomena are not missed. Similarly, constraining global network approaches to networks defined by key anatomical pathways may be a promising way forward to determine the nature of functional connectivity abnormalities in networks previously shown to be structurally abnormal in BD. In parallel, examining within-subject variability over time in functional connectivity *a priori*, localized neural networks may identify more consistent patterns of abnormal temporal dynamics within these networks in individuals with BD, and help clarify some of the apparent discrepant observations within the literature.

Another potential source of discrepancy in findings from functional connectivity studies in BD is the inclusion, in many cases, of different diagnostic groups in different mood states. This may have narrowed focus in individual studies to different phenotypes and mood states, with different underlying neural network abnormalities, making findings across studies difficult to harmonize. Thus, in parallel with adoption of the above-described rational approaches to examine *a priori* neural networks described above, future studies could also include individuals across the bipolar disorder spectrum, in either euthymic, depressed or hypo/manic mood states, to focus on the same broader —bipolar|| phenotype, help identify mood state-independent abnormalities. The potential effects of psychotropic medication upon connectivity also need further investigation.

The above directions represent first steps to harmonize methodological approaches across studies to facilitate a better understanding of neural network functional connectivity abnormalities that characterize BD. Further steps that need to be made to elucidate neural network functional connectivity abnormalities in the disorder include examination of networks across bipolar and other disorders, and examination of networks over development in youth with, and youth at risk for, bipolar disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Description of putative functional interactions between the amygdala, medial and ventrolateral regions of the PFC. We posit that altered connectivity between the ventrolateral regions and the amygdala is specific to BD, whereas the medial PFC may play a mediating role, as well as providing independent control of the amygdala. Possible interactions of this circuitry with other regions are noted.

Table 1

Studies of prefrontal cortical-amygdala / prefrontal cortical-ventral striatal / within prefrontal cortex functional connectivity during a challenge task using fMRI. BD=bipolar disorder (types I and II if known); SZ=schizophrenia; MDD=major depressive disorder (unipolar); HC=healthy control participants. DCM=dynamic causal modeling; ICA=independent components analysis. The column named “Altered Connection” briefly summarizes the implication of the paper in terms of one of the connections of main interest (mPFC/vlPFC/amygdala relationships), or notes whether the findings of the study pertain to another circuit.

Publication	Regions examined	Participant group(s)	Design / Paradigm	Findings	Altered Connection
Almeida et al., 2009 (16)	DCM; Central OFC, Amygdala	BD I depressed; MDD; HC	Cross sectional; Emotional face processing	BD&MDD reduced left sided OFC → amygdala connectivity during happy faces, also trend during sad faces; BD reduced right sided amygdala → OFC during happy faces vs MDD/control	Amygdala – mPFC (BD reduced)
Almeida et al., 2009 (73)	DCM: Parahippocampal gyrus (PHG); sgACC; DLPFC ROIs	BD I Euthymic, HC	Cross sectional; Emotional face processing	Enhanced connectivity between PHG and sgACC in BD; no difference between sgACC/DLPFC connectivity	<i>Within PFC</i>
Breakspear et al., 2015 (33)	DCM: Fusiform, ACC, IFG, DLPFC	BD, at risk (first degree relatives), HC	Cross sectional; Emotion and non-emotion Go-No Go	Hierarchical models established with DLPFC and ACC providing input into IFG. At risk group show altered modulation of DLPFC to IFG by ACC.	vlPFC-mPFC (interactions modulated in at risk group); <i>Within PFC</i>
Caseras et al., 2015 (34)	Seed based: DLPFC/Amygdala/ VS PPI	BD I and II Euthymic, HC	Cross sectional; WM paradigm with emotional face distractors	Enhanced inverse DLPFC/amygdala coupling in BD II compared to BD I& controls during fear; No differences in DLPFC/VS coupling during happy faces	<i>Amygdala – Other PFC</i>
Cerullo et al., 2012 (74)	Seed based, amygdala seed, wholebrain target	BD I manic and BD I depressed (and HC)	Longitudinal , within-subjects design (manic first, then depressed; 1 year between scans) , cognitive-emotional task	Differential patterns of right amygdala-PFC FC in manic and depressed BDI – more positive right amygdala-left IFC FC in manic; more positive right amygdala-right insula FC in depressed.	Amygdala – vlPFC (BD increased)
Dima et al., 2013 (14)	DCM: occipital, fusiform, VLPFC, amygdala ROIs	BD Euthymic, HC	Cross sectional; Emotional face processing; CACNA1C/AN	BD show emotion-modulated amygdala→	Amygdala – vlPFC (emotion

Publication	Regions examined	Participant group(s)	Design / Paradigm	Findings	Altered Connection
			K3 genotype	vIPFC and weaker occipital→vIPFC connectivity; controls show emotion modulated occipital→VLPFC connectivity	modulated in BD not controls)
Favre et al., 2015 (75)	Seed based: right DLPFC, whole brain target	BD Euthymic, HC	Cross sectional; emotional face/word Stroop paradigm	BD show greater connectivity between right DLPFC and sgACC, precuneus/PCC and left SFG	<i>Within PFC</i>
Foland et al., 2008 (76)	Seed based, left amygdala seed, wholebrain target	BD I (manic, hypomanic), HC	Cross sectional; Emotional labelling task	BD showed less negative connectivity between left amygdala and bilateral vIPFC than HC; BD showed more negative connectivity between left amygdala and ACC and right rostral PFC than HC	Amygdala-vIPFC (less negative in BD) Amygdala-mPFC (more negative in BD)
Horacek et al., 2015 (15)	Seed based, amygdala seed, wholebrain target	Remitted BDI, HC	Cross sectional design. Sad and neutral mood induction prior to viewing sad and neutral faces	BDI: sad (vs neutral) mood induction increased FC between amygdala and vIPFC to sad faces HC: such mood induction decreased FC between these regions to sad faces	Amygdala – vIPFC (group by mood interaction)
Kanske et al., 2015 (77)	Seed based, amygdala seed, prefrontal cortical and parietal cortical target	Euthymic BDI, unaffected first degree relatives of BDI probands, two groups of age- and education-matched HC	Cross-sectional design. Emotion regulation task - re-appraisal and distraction strategies	HC: inverse FC between amygdala and VLPFC/OFC during re-appraisal; BD: positive FC between these regions during re-appraisal. No significant differences in FC between these regions in first-degree relatives of BD probands	Amygdala – vIPFC (increased in BD)
Marchand et al., 2014 (37)	Seed based: medial SFG (left/right)	BD II Euthymic, HC	Cross sectional; motor paradigm	BD show enhanced connectivity with left SFG and right MFG	<i>Within PFC</i>
Mason et al., 2014 (39)	ROI-based; examination of between- participant regional intercorrelations (VS/vmPFC/DLPFC	BD Euthymic, HC	Cross sectional; Risk taking paradigm	Reduced coupling between vmPFC and DLPFC in BD; mania symptoms associated with	<i>Within PFC / VS-PFC</i>

Publication	Regions examined	Participant group(s)	Design / Paradigm	Findings	Altered Connection
	)			enhanced VS/vmPFC coupling	
Morris et al., 2012 (78)	ROI based: left vIPFC and amygdala	BD I (predominantly euthymic or hypomanic), SZ, HC	Cross sectional; emotion-regulation paradigm	Change in left vIPFC activation during emotion down-regulation negatively associated with amygdala activation in HC, whereas activation between regions uncorrelated in BD/SZ	Amygdala – vIPFC (less negative in BD)
Mullin et al., 2012 (79)	Seed based—amygdala seed, wholebrain target	BD I euthymic, HC	Cross sectional; n-back task with emotional distractors	Reduced connectivity between ACC and amygdala in BD compared to HC with fear distractors, greater connectivity between same regions with happy distractors.	Amygdala – mPFC
Perlman et al., 2012 (25)	Seed based—amygdala seed, wholebrain target	Remitted BDI, depressed BDI, HC	Cross-sectional design. Emotional face processing task	Differential patterns of amygdala-PFC FC in BDI remitted and BDI depressed (vs. HC)	Amygdala-mPFC (mood dependent)
Pompei et al., 2011 (30)	Seed based - -vIPFC seed, wholebrain target	Euthymic BDI, first degree relatives with MDD, first degree healthy relatives, HC	Cross sectional design. Stroop color word task	BDI and relatives: reduced inverse vIPFC-vACC FC (vs. HC). BDI –abnormal vIPFC-insula positive FC, relatives - - reduced inverse vIPFC-insula FC (vs. HC)	vIPFC – mPFC (less negative in BD)
Radaelli et al., 2015 (80)	DCM: ROIs included DLPFC, ACC, Amygdala (left side regions chosen)	BD I depressed, HC	Cross-sectional design. Emotional faces paradigm.	Similar model structure between groups; BD show a reduced connection from DLPFC to amygdala compared to HC.	<i>Amygdala – Other PFC</i>
Townsend et al., 2013 (12)	Seed based, amygdala seed, PFC target regions	Euthymic BDI, HC	Cross sectional design. Emotional regulation task - -passive viewing and emotional downregulation conditions	HC>BDI: significantly greater inverse bilateral vIPFC-left amygdala FC during emotional downregulation BDI>HC: significantly greater inverse FC between right amygdala and right mPFC (BA 9)	Amygdala – vIPFC (less negative in BD) Amygdala – mPFC (more negative in BD)
Trost et	Seed based, VS	BD euthymic	Cross sectional	BD: significantly	<i>VS - PFC</i>

Publication	Regions examined	Participant group(s)	Design / Paradigm	Findings	Altered Connection
al., 2014 (40)	seed, PFC regions target	and depressed, HC	design, desire-reason dilemma reward task	reduced inverse FC between VS and avPFC during successful suppression of response to reward cues (vs. HC)	
Vai et al 2015 (81)	DCM: ROIs included DLPFC, ACC, Amygdala, Fusiform Gyrus, Visual cortex	BD I depressed, HC	Two sessions: pre and post treatment (total sleep deprivation & light therapy). Emotional faces paradigm	Relatively similar model structure in all patients. In treatment responders, interactions between DLPFC and ACC increased after treatment, while task modulation of Amygdala→DLPFC interaction decreased.	<i>Within PFC / Amygdala – Other PFC</i>
Versace et al., 2010 (17)	Seed based: amygdala and OFC regions	Remitted BDI, depressed BDI, HC	Cross sectional design. Emotional face processing task	All BDI: significantly greater right amygdala-OFC FC to sad faces. Depressed BDI (but not remitted BDI) showed increased left amygdala-OFC FC to sad faces, and reduced bilateral amygdala-OFC FC to intense happy faces.	Amygdala – mPFC (mood dependent findings)
Vizueta et al., 2012 (82)	Seed based: amygdala seed, whole brain target	Depressed BDII, HC	Cross sectional design. Emotional face matching task	BDII: significantly greater positive connectivity between right amygdala and left VLPFC than HC; significantly reduced inverse FC between right amygdala and right rostralateral dlPFC than HC;	Amygdala –vLPFC (more positive in BD) <i>Amygdala – Other PFC</i>
Wang et al., 2009 (18)	Seed based, pregenual ACC seed, wholebrain target	Manic, depressed and euthymic BD, HC (specific types not specified)	Cross sectional design. Emotional face processing task	BD: significantly decreased pregenual ACC-amygdala FC to fearful and happy (but not neutral) faces (vs. HC)	Amygdala –mPFC (decreased in BD)

Table 2

Studies of prefrontal cortical-amygdala / prefrontal cortical-ventral striatal / within prefrontal cortex functional connectivity using resting fMRI. GU = glucose utilization

Publication	Regions examined	Participant group(s)	Design / Paradigm	Findings	Altered Connection
Anand et al., 2009 (24)	ROIs including amygdala, pgACC, thalamus, striatum	BD (manic/depressed), MDD, HC	Cross-sectional design	BD showed reduced connectivity between pgACC and thalamus/striatum/amygdala ; Weaker reductions in same networks also seen in MDD.	Amygdala – mPFC (reduced in BD)
Anticevic et al., 2013 (22)	Global PFC connectivity and seed based: amygdala/ whole PFC target	BD with and without psychosis history, HC	Cross-sectional design	Amygdala/mPFC, amygdala/ dmPFC and global PFC/mPFC connectivity altered in BD with psychosis history but not clearly in patients without such history	Amygdala – mPFC (increased in BD with psychosis history)
Anticevic et al., 2015 (23)	Seed based: vmPFC, whole brain target	BD with and without psychosis history, HC (also SZ)	Cross-sectional design	BD without psychosis history show heightened vmPFC / dmPFC connectivity compared to HC and patients with psychosis history	<i>Within PFC</i>
Chai et al., 2011 (27)	Seed based: mPFC seed, whole brain target	BD, SZ and HC	Cross-sectional design	BD—positive FC between mPFC and vlPFC and between mPFC and anterior insula. HC - -inverse FC between the regional pairs. Sz – no significant FC between these regional pairs. HC only showed inverse FC between mPFC and dlPFC	mPFC – vlPFC (less negative in BD)
Chepenik et al., 2010 (28)	Seed based, vPFC seed (relatively lateral); amygdala/ wholebrain target	Euthymic, hypo/manic and depressed BD and HC	Cross-sectional design	HC: inverse FC between left vPFC and left amygdala - -greater than in BD. Higher positive FC between left vPFC and right vlPFC/ ACC and right VS in BD vs. HC.	Amygdala – vlPFC/mPFC (less negative in BD; vPFC ROI extends from x =-33 to -17) mPFC - vlPFC (more positive in BD)
Favre et al., 2014 (83)	Seed based, mPFC seed; amygdala/ wholebrain target	Euthymic BD and HC	Cross-sectional design	BD: greater positive FC between mPFC and amygdala (than HC); significant inverse FC between	Amygdala – mPFC (more positive in BD)

Publication	Regions examined	Participant group(s)	Design / Paradigm	Findings	Altered Connection
				mPFC and right dIPFC in HC NOT found in BD.	
Li et al., 2015 (19)	Seed based, bilateral amygdala seeds, wholebrain target	Manic BD, depressed BD, HC (presume BDI, but not explicitly stated)	Cross-sectional design	Main finding: REDUCED FC between bilateral amygdala and OFC, VS in BD mania and BD depressed vs. HC (Also—right amygdala-hippocampal FC increased in BD manic, decreased in BD depressed).	Amygdala – mPFC (reduced in BD)
Li et al., 2015 (36)	Seed based: DLPFC (seed), amygdala (target)	BD Euthymic; Unaffected siblings; HC	Cross-sectional design; PET data (glucose utilization) also acquired	BD show reduced inverse connectivity between DLPFC and amygdala; similar but weaker effect in sibs. BD but not sibs also show reduced DLPFC and enhanced amygdala GU = glucose utilization.	<i>Amygdala – Other PFC</i>
Liu et al., 2014 (20)	Seed based: Amygdala (each subregion assessed independently), whole brain target	BD, SZ, HC	Cross-sectional design.	BD show reduced connectivity between different amygdala subregions and mPFC regions (also mid cingulate / rostral PFC) relative to HC. Comparison of SZ and BD yielded mixed findings, but mPFC/amygdala connectivity was also greater in SZ compared to BD.	Amygdala – mPFC (reduced in BD)mPFC (reduced in BD)
Magioncalda et al., 2015 (29)	Seed based: pgACC / whole brain (also dorsal ACC/PCC seeds used).	BD (manic / depressed / mixed / euthymic), HC	Cross-sectional design. Different frequencies assessed (0.01-0.1Hz; 0.010.027Hz; 0.0270.073Hz)	Reduced connectivity (esp. low frequencies) between dACC and pgACC, also left VLPFC/OFC and right DLPFC. Other abnormalities observed in posterior regions.	mPFC – vIPFC (reduced in BD)
Oertel-Knochel et al., 2015 (84)	Seed based vs whole brain: Left SFG; bilateral IFG; bilateral parahippocampal gyrus; bilateral precuneus.	BD Remitted, HC	Cross-sectional design. Resting state fMRI.	BD show reduced connectivity between left SFG and bilateral anterior mPFC, left SFG and MTL and enhanced connectivity between left SFG and ACC relative to HC; BD show reduced connectivity	<i>Within PFC</i>

Publication	Regions examined	Participant group(s)	Design / Paradigm	Findings	Altered Connection
				between IFG and hippocampus relative to HC.	
Ongur et al., 2010 (85)	Default mode identification using ICA	BD (Manic/Mixed), SZ, HC	Cross-sectional design	Altered spatial extent of DMN in BD and SZ. DMN of BD reduced vs HC in medial PFC and Hippocampus but enhanced in lateral frontal pole and parietal. Association of PCC with YMRS scores.	Within PFC
Satterthwaite et al., 2015 (38)	Network-based analysis of reward-related regions including PFC / thalamus / VS / VTA	BD depressed, MDD, HC	Cross-sectional design	Depression severity (BD&MDD) reduced connectivity between VS&thalamus and vmPFC&VTA;	<i>mPFC - VS</i>
Torrisi et al., 2013 (31)	ROI-based: bilateral vlPFC/amygdala; Seed based: right amygdala, whole brain	BD euthymic, HC	Cross-sectional design	Enhanced right amygdala / right VL PFC connectivity. mPFC plays mediating role	Amygdala – vlPFC (increased in BD)
Wang et al., 2015 (86)	Whole brain: voxel mirrored homotopic connectivity	BD II depressed, HC	Cross-sectional design	Reduced inter-hemispheric connectivity in anterior mPFC and inferior temporal gyrus	<i>Within PFC</i>