Brain networks in bipolar disorder II: A resting-state fMRI study

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Abstract

Bipolar disorder II (BD-II) is characterized by hypomanic and depressive episodes, accompanied by mild cognitive deficits, which can be postulated to be due to emotional and cognitive dyscontrol, with attention as the binding factor. Structural and functional magnetic resonance imaging (fMRI) have implicated several brain regions across the BD spectrum, including the prefrontal cortex (PFC), cingulate cortex and amygdala. Newer studies also look at whole brain networks using resting-state fMRI (RS-fMRI). A notable RS network is the default-mode network (DMN), typically activated at rest and associated with mind wandering. The aim of the current study was to characterize functional brain networks specifically in BD-II patients (n = 32) by assessing of within and between network connectivity against healthy controls (n = 35) through RS-fMRI (age 18-50). We also assessed the subjects on working memory measures using the RAVLT and BVMT-R. Independent component analysis and dual regression was used for within-network analysis, and FSLNets was used for between-network connectivity and network modeling. Based on earlier findings, we predicted aberrant connectivity within the DMN, increased connectivity within the anterior cingulate cortex, decreased connectivity between the ventrolateral PFC and amygdala, and decreased connectivity between the posterior cingulate cortex and DMN. We also expected visual networks to display increased connectivity to the amygdala. Decreased test performance was observed on the BVMT-R, and decreased delayed recall on the RAVLT. We found no statistically significant changes in connectivity within or between networks, indicating that brain networks in BD-II are not significantly different from healthy individuals.

Keywords: rs-fMRI, BD-II, resting-state networks, DMN, PFC, ACC, amygdala, ICA, dual regression, network modeling, within-network connectivity, between-network connectivity, clustering hierarchy

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Introduction

Mood disorders are one of the most pervasive and disabling disorders (World Health Organization, 2003)**.** Despite the fact that standards of living have substantially improved over the past few centuries, the number of people diagnosed with mood disorders has increased exponentially (National Institute of Mental Health, 2008). One of the most debilitating mood disorders is bipolar disorder (BD), and the World Health Organization (WHO) regards BD as one of the leading causes of disability worldwide (Murray & Lopez, 1996). BD is characterized by acute dysfunctional mood states, alternating between mania (BD-I) or hypomania (BD-II) and depression (Vieta & Suppes, 2008). This is partly a result of an inability to regulate emotion. A person diagnosed with BD that is not having a depressive or (hypo)manic episode is said to be euthymic. There is a higher prevalence of depressive compared to hypomanic symptoms during the course of BD, which makes it difficult to distinguish BD from unipolar depression (UD), also known as major depressive disorder (MDD). This is further impeded by subthreshold manic symptoms during a depressive episode (Judd et al., 2012). The heterogeneous clinical expression of bipolar spectrum disorders suggests that BD actually consists of several subcategories, in particular BD-I, which is characterized by both depressive and full-blown manic episodes, and BD-II, characterized by depressive and hypomanic episodes (Vieta & Suppes, 2008). Another important distinction is that BD-I individuals are more likely to have a history of psychotic symptoms, in particular during manic phases (Vieta & Suppes, 2008).

Most studies investigating the neurobiological mechanisms of bipolar spectrum disorders have not differentiated between subcategories, partly due to the difficulty in recruiting enough patients in the different sub-groups (Townsend & Altshuler, 2012). Most studies have focused on BD-I, which by many is still regarded as prototypical of the bipolar spectrum disorders. Thus, accumulated evidence about the underpinnings of BD mostly pertains to the BD-I category. In contrast, BD-II has received little attention in the neuroscientific BD literature, likely partly because BD-II is regarded a less debilitating disorder than BD-I, but also because a smaller percentage of those afflicted with BD have the BD-II subtype (Townsend & Altshuler, 2012). The estimated lifetime prevalence is 0.6% for BD-I (male predominance) and 0.4% for BD-II (female predominance; Merikangas & Lamers, 2012). Typically, BD symptoms first present in adolescence or preadolescence, with a mean age of onset at 18 years, usually manifested as exacerbated mood swings (Merikangas et al., 2011). Unfortunately, the gap between symptom onset and diagnosis may be as long as 10 years (Hirschfeld, Lewis, & Vornik, 2003; Suppes et al., 2001).

BD-II is likely more recurrent than BD-I, with more (hypo)manic and depressive episodes than in BD-I (Vieta & Suppes, 2008). Major depressive episode (MDE) symptoms that are more common in BD-II than UD are weight gain, increased eating, hypersomnia, psychomotor agitation, worthlessness, and diminished ability to concentrate (Benazzi, 2006). Although the manic and depressive symptoms are quite different, they can co-occur giving rise to "mixed-states" (Anderson, Haddad, & Scott, 2012). Moreover, deliberate self-harm occurs in 30-40% of patients, and could be related to the depressive and mixed episodes (Novick, Swartz, & Frank, 2010).

Hypomania is essentially a shorter and less severe form of mania, and is not necessarily seen as a barring symptom. Indeed, the patient may view hypomania as having a positive effect on their lives, and as such some will refrain from seeking medical attention (Anderson et al., 2012). Indeed, despite experiencing a greater number of episodes than BD-I, people with BD-II are hospitalized less frequently (Vieta & Suppes, 2008). Common hypomanic symptoms include overactivity, distractibility, racing/crowded thoughts, irritable mood, psychomotor agitation, more talkativeness, risky activities and increased goal-directed activity (Benazzi, 2006). Subthreshold symptoms of hypomania are present in 30% to 55% of individuals during a depressive episode (Angst et al., 2010; Judd et al., 2012). A subset of these, hypersomnia, racing/crowded thoughts, irritability and psychomotor agitation have been shown to be the best predictors of BD-II (for hypomania; Perlis et al., 2006). Nevertheless, whether there are different dimensions of hypomania is debated, and as such, people with BD-II can be misdiagnosed with UD (Ghaemi, Boiman, & Goodwin, 2000). Indeed, clinical symptoms of BD-II and UD have been suggested to reflect different levels along the same pathophysiological continuum (Benazzi, 2003).

In a study over a 6 month period (Torrent et al., 2006) , BD-II patients showed persistent cognitive deficits (through a variety of neuropsychological tests) compared to healthy controls but to a lesser degree than those with BD-I. BD-II patients had higher number of perservative errors on the Wisconsin Card Sorting Test (WSCT; executive functions), indicating impaired memory and executive functioning. Patients also showed intermediate performance on the Stroop interference tasks and California Verbal Learning Test (CVLT), and performed particularly poor on measures related to semantic verbal fluency (animal naming) and verbal learning and memory on the CVLT. Secondly, longer illness duration of BD-II was associated with more slowness or diminished attention as revealed by the Trail Making Test-A (TMT-A). Despite the fact that BD-II individuals exhibited cognitive

dysfunctions relative to the healthy control group, the effect sizes were medium (Torrent et al., 2006).

One could stipulate that BD-II is encompassed by emotional and cognitive dyscontrol, which could account for the depression symptoms and cognitive deficits (which could be linked with hypomania). One common factor they share is attention, which hypothetically could affect both of them. This is inherently connected to certain brain structures, which will be discussed further below. One method of evaluating brain regions is through structural methods, which are important for the development of appropriate treatment regimens that can differentiate BD-II from BD-I and other mood disorders. This involves assessing change in various measures including cortical thickness and volume of specific structures.

Structural brain changes in BD

For a good overview of structural studies of BD, Emsell and McDonald (2009) provide an excellent review on structural neuroimaging studies of BD. Notable discrepancies in structural imaging studies of BD exists, likely partly due to the differences in methods being used, e.g. full-brain voxel-based morphometry (VBM) contra region of interest (ROI) analysis (Emsell & McDonald, 2009). For instance, some studies have shown smaller prefrontal cortex (PFC) in BD patients, while others have not (Strakowski, DelBello, Adler, Cecil, & Sax, 2000). Also, several studies have found distributed regional grey matter (GM) volume reduction in the cingulate gyrus, frontal and temporal regions in BD-I patients (Lyoo et al., 2004; Nugent et al., 2006; Wilke, Kowatch, DelBello, Mills, & Holland, 2004). In contrast, some studies have shown no difference when compared with healthy controls (McDonald, Bullmore, et al., 2006), and some where there are both GM increases and decreases (Adler et al., 2007).

Two important nodes of the emotional processing network are the medial PFC (mPFC) and the ventral PFC (VPFC; Elliot et al., 2004). Importantly**,** mPFC plays a role in regulating emotion (Anticevic et al., 2012) through its connections with other subcortical structures (e.g. amygdala; Price, Carmichael, & Drevets, 1996). There is evidence of GM decrease in the dorsolateral prefrontal cortex (DLPFC; Farrow, Whitford, Williams, Gomes, & Harris, 2005), where one study found reduced GM volume in the left DLPFC (Dickstein et al., 2005). Another structure involved in emotion regulation is the anterior cingulate cortex (ACC; Bush, Luu, & Posner, 2000). Several studies have found reduced GM and cortical thickness in the left ACC (Lyoo et al., 2004; Lyoo et al., 2006; Womer, Kalmer, Wang, & Blumberg, 2009). Nonetheless, the results vary considerably, and, other studies have found an increase

(Javadapour et al., 2007), bilateral decrease (Farrow et al., 2005), left-sided decrease (Kaur et al., 2005), and no changes in ACC volume (Fornito et al., 2008).

Structural studies on the amygdala have also produced mixed findings, with increased amygdala volume in BD-I and BD-II patients (Brambilla et al., 2003) and decreased amygdala volume in BD-I patients (Blumberg et al., 2005) being reported. In another study, decrease was found in the left amygdala with less conservative statistical thresholding (Dickstein et al., 2005) and some studies found no difference in amygdala volume for juvenile patients (Frazier et al., 2005; Frazier et al., 2007). A recent study on medication-free BD patients (Foland-Ross et al., 2012) using three-dimensional mapping, found no change in amygdala structure due to BD, although they found a significant interaction of age and BD, indicating detriment over time as BD worsens. The lack of main effect of diagnosis indicates that amygdala reveal no structural abnormalities in the absence of lithium or acute mood state. This is consistent with a recent review on the effects of psychotropic medication on structural MRI measures (Hafeman, Chang, Garrett, Sanders, & Phillips, 2012), where they find that lithium in particular increases the volume of areas important in emotional processing (i.e. the amygdala).

Compared to other subcortical structures, hippocampus volume seems to be preserved in BD (Strakowski et al., 2000) compared to UD. This relates to a mixed BD group, so one can stipulate that there will be even less volume reduction in patients with BD-II (Cousins & Grunze, 2012). Very few studies show hippocampal decrease (e.g. Blumberg, Kaufman, et al., 2003; Dickstein et al., 2005; Frazier et al., 2005), most show a preservation of hippocampal volume (e.g. McDonald, Marshall, et al., 2006), the latter being supported by a meta-analysis of 200 patients with BD (McDonald et al., 2004). Despite this, one study (Rimol et al., 2010) found considerable volume reductions bilaterally in the hippocampus in BD-I patients. A recent study (Foland-Ross et al., 2012) found no differences in hippocampal volume in patients not treated with lithium. Another recent study (Elvsåshagen et al., 2013) investigated the volume of hippocampal subfields in patients with BD-II. This includes the dentate gyrus (DG), subiculum, entorhinal cortex and cornu ammonis (CA) 1 to 4. The current study and the one by Elvsåshagen and co-workers (2013) are part of the same project, with overlapping participants. The changes were subtle, with the left and total DG-CA4 volume decreased by 5.4%, while the left and total fimbria volume decreased by 12.0% in BD-II patients compared to healthy controls.

In summary, most subcortical structures show no unity in structural change in BD-II patients. Mixed findings have been found for structural change in the PFC (e.g. Strakowski, et

al., 2000), ACC (e.g. Fornito et al., 2008; Javadapour et al., 2007) amygdala (e.g. Blumberg et al., 2005; Brambilla et al., 2003), and a tendency for decrease in the hippocampus (Elvsåshagen et al., 2013; Rimol et al., 2010). A step further in the neurobiology of BD-II, is to investigate the functions of said structures.

Functional brain changes in BD

Brain structure and function are inherently linked and jointly contribute to our behavioural responses (Johansen-Berg, 2009), although the degree to which can vary across levels of cognitive processing (Tahmasebi et al., 2012). For instance, Kalmar and colleagues (2009) found increased amygdala response in BD patients in response to emotional faces, as well as a decrease in amygdala volume.

One of the most recurring findings when comparing manic patients to healthy subjects, is excessive amygdala activation in response to faces (Strakowski et al., 2012). A meta-analysis (Chen, Suckling, Lennox, Ooi, & Bullmore, 2011) found increased amygdala activation in euthymia when looking at ROI studies, supported by Hulvershorn and coworkers (2012), where a negative facial emotion matching task was employed. In a large meta-analysis (Kupferschmidt & Zakzans, 2011) including fifty-five functional neuroimaging studies, limbic regions exhibited hyperactivity on average in BD patients relative to healthy controls. This was most pronounced at rest or while conducting facial affect tasks (De Almeida, Versace, Hassel, Kupfer, & Phillips, 2010). This contrasts with a recent study where depressed non-medicated BD-II patients showed reduced right amygdala activation while doing an emotional face-matching task (Vizueta et al., 2012). Notably, this latter study is one of the few studies which specifically included a BD-II group and there is considerable disparity of studies showing activation or deactivation in BD patients during depressive episodes (Strakowski et al., 2012). While this is the case, most studies show some form of activation differences between cases and healthy controls in the amygdala (C. H. Chen et al., 2011), suggesting that amygdala dysfunction is a key feature in BD. Amygdala dysfunction also seems to be a trait in patients during periods of mania (Strakowski et al., 2012).

A consistent finding in studies of BD patients during mania using cognitive and emotional tasks are reduced activation in the VPFC (Altshuler et al., 2005; Blumberg et al., 2003; C. H. Chen et al., 2006; C. H. Chen et al., 2011; Cousins & Grunze, 2012; Elliot et al., 2004; Strakowski et al., 2012), which encompasses the orbito-frontal cortex (OFC), ventrolateral prefrontal cortex (VLPFC) and ventromedial prefrontal cortex (VMPFC). This

includes BD patients during mania while doing a continuous performance task with emotional and neutral distracters (Strakowski et al., 2011) and one with an emotional faces task (Foland et al., 2008). Recently, significant reduction in activation was found in bilateral VLPFC in depressed BD-II patients (Vizueta et al., 2012). This is of importance, because the VLPFC has been shown to play an inhibitory role over the amygdala in healthy subjects (Hariri, Bookheimer, & Mazziotta, 2000), which is shown to be aberrant in BD-II patients. Importantly, BD depression differentiates from BD mania, where increased activation is observed rather than deactivation (C. H. Chen et al., 2006; Lawrence et al., 2004). A meta-analysis showed that BD patients on average exhibited hypoactivity in frontal regions compared to healthy controls (Kupferschmidt & Zakzans, 2011). This was most pronounced when they were imaged at rest or while conducting facial affect tasks. In another study (Hulvershorn et al., 2012) emotional-facial task, increased activation was found in the DLPFC for BD patients during mania compared to healthy controls, BD patients during euthymia and depressed BD patients. In the same study, decreased activation was found in the left lateral OFC in BD patients during mania compared to BD patients during euthymia and healthy controls. Also, the OFC was decreased in BD patients across states in response to happy and neutral faces compared to healthy controls (J. Liu et al., 2012). In the same study, increased activity was found in the left OFC in response to fearful faces for depressed BD-patients (J. Liu et al., 2012). The OFC is important in the assessment of emotional significance and reward potential of stimuli (Ongur & Price, 2000).

In several studies, ACC activation was increased in BD subjects during mania compared to healthy controls, and activation was decreased during BD depression (Hulvershorn et al., 2012; Marchand et al., 2007; Strakowski et al., 2008; Wessa et al., 2007), specifically in the dorsal portion (dACC) for one study (Hulvershorn et al., 2012). The dACC has often been linked to cognitive function (Mohanty et al., 2007), which can be under-activated during euthymia (Pavuluri, O'Connor, M., & Sweeney, 2008). In contrast, the rostral (rACC) has been linked to emotional function (Mohanty et al., 2007) which can be over-activated during euthymia (Gruber, Rogowska, & Yurgelun-Todd, 2004). Another study utilizing an n-back working-memory paradigm showed elevated dorsal anterior midcingulate cortex activity in the UD group during the emotional n-back tasks with neutral face distracters relative to BD individuals and healthy controls (Bertocci et al., 2012). Lastly, C. H. Liu et al. (2012) reported that ventral (vACC) activity was decreased in the BD group in response to happy and neutral faces across mood state, relative to the healthy control group.

Summarized, the functional imaging literature on BD disorders has provided heterogeneous findings, even when accounting for the differences in episodes and mood states. Different activation patterns has been found in the amygdala (e.g. Strakowski et al., 2012), the VPFC (e.g. Cousins & Grunze, 2012) , the DLPFC (e.g. Hulvershorn et al., 2012) and the OFC (e.g. J. Liu et al., 2012) . However, findings concerning the ACC are more homogenous, with increased activation in the dACC during a cognitive task (e.g. Bertocci et al., 2012). These neuroimaging studies of BD have involved several different task paradigms (Hulvershorn et al., 2012)**,** which highlights the importance of singular structures, but does not consider brain structures in a network, highlighting functional interdependence. The next step is to look at brain networks, the connectivity within and between them.

Resting-state networks (RSNs)

Energy consumption of the brain is only slightly higher (1-5%) for the brain during an active task than when at "rest" (Raichle & Gusnard, 2002; Raichle & Mintun, 2006). In addition, the metabolic demand of spontaneous activity consumes more that 80% of the brain's energy (Raichle, 2010), suggesting that specific task-related cognitive processing consumes only a fraction of the brain's energy (Rosazza & Minati, 2011). This has fuelled an explosive interest in rs-fMRI, representing a paradigm shift in neuroimaging studies. Rs-fMRI targets the intrinsic brain patterns while participants are being scanned at "rest" (Biswal, Yetkin, Haughton, & Hyde, 1995). This enables one to look at the resting-state functional connectivity (RSFC) within networks, which is essentially the co-activation of any region within a network. One of the main tenets of rs-fMRI is the ability to investigate how multiple regions of the brain interact with each other, allowing for a network perspective of the brain (Rosazza & Minati, 2011).

Notwithstanding, the exact functions of these spontaneous activities are unknown. One possibility is that they reflect spontaneous cognitive processes (Rosazza & Minati, 2011), which ties with the default-mode network (DMN), although it is not likely the only source. These spontaneous activities are seen across behavioural states and resting conditions (Van Dijk et al., 2010) and task performance (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006). It follows that they can also be seen in different states including sleep (Horovitz et al., 2009) and in disorders of consciousness (Rosazza & Minati, 2011; Vanhaudenhuyse et al., 2010). Among several promising aspects of resting-state fMRI research is its clinical application, which is partly due to the simplicity of the data collection procedure (i.e. no specific task-demands) and that it can be used across disorders.

DMN

A prominent resting-state network is the DMN, which is found almost consistently across resting-state/brain network neuroimaging studies (Harrison et al., 2008). The DMN consists of the posterior cingulate cortex (PCC), mPFC, and the inferior, medial and lateral parietal cortex. In addition, the ACC can be considered part of the DMN (Sheline et al., 2009). The DMN is known to be activated during rest, and attenuated during task-specific activities (Raichle et al., 2001). The degree of deactivation increases with the demands of a task (McKiernan, D'Angelo, Kaufman, & Binder, 2006). The DMN has been linked to introspective mental processes, and the tendency to mind wander (Mason et al., 2007), and contemplating our recent past and to imagine future events (Buckner, Andrews-Hanna, & Schacter, 2008). Other studies have suggested that the DMN is also active when attention is not directed towards external stimuli. Rosazza and Minati (2011) have noted that during task-fMRI, the activity of the DMN is increased when participants made a slow response or were distracted (C. S. Li, Yan, & KL, 2007; Weissman, Roberts, Visscher, & Woldorff, 2006).

The DMN has been suggested to play a critical role in the neural circuitry mediating BD depression (Calhoun et al., 2012; Ongur, Lundy, Greenhouse, Shinn, & Menon, 2010). Decreased functional interaction in limbic regions and increased functional interaction in other cortical regions could relate to the dysregulated emotional processing and increased goal directed activities seen in mania (Strakowski, DelBello, & Adler, 2005). The DMN plays a central role in monitoring the external environment, which could connect to some behavioural aspects of BD (Calhoun et al., 2012), such as diminished attention. Nevertheless, it also seems to be involved in working-memory, where some studies (e.g. Hampson et al., 2006) found the PCC and medial frontal gyrus to be functionally connected during a working-memory task. This implies that rather than just being deactivated, the DMN may assist or monitor performance of active tasks (Buckner, 2012). Furthermore, the DMN is not constrained to human subjects, extending to anesthetized monkeys (Vincent et al., 2007). Although it may just be an overlap in brain regions, it suggests that there are commonalities of brain networks across species (Rosazza & Minati, 2011), supporting an important role in brain function (Buckner, 2012).

The precuneus/PCC, mPFC and lateral areas, are strongly inter-correlated, forming the core of the DMN (Buckner et al., 2008; Fransson & Marrelec, 2008). The PCC has interconnections with many brain regions (Cavanna & Trimble, 2006; Hagmann et al., 2008), and has been suggested to mediate the intrinsic DMN connectivity, thus acting as an important hub of the DMN (Buckner, 2012). This is supported by a review pointing to the

PCC's role in introspective processes and awareness (Buckner et al., 2008). The medial frontal gyrus is another hub of the DMN, which is important for decision making, generating expectations, and the ability to assess affective value of reinforcers (Kringelbach, 2005). The medial frontal gyrus is also involved in both emotion perception and cognitive regulation functions (Chai et al., 2011) and functional alterations in the medial frontal gyrus thus could be associated with the cognitive-emotional aberrance in BD (C. H. Liu, X. Ma, F. Li, et al., 2012). DLPFC activation is associated with external attention and executive control, while activation in the mPFC is suppressed (Greicius, Kransow, Reiss, & Menon, 2003; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Rosazza & Minati, 2011). Decreased network-level connectivity in the DMN has been found in people suffering from mild cognitive impairment (MCI; Rosazza & Minati, 2011; Sorg et al., 2007).

Other RSNs of interest

Other common RSNs relevant to BD are visual networks (Y. Chen et al., 2006) .Using a database (BrainMap) of task-based neuroimaging studies, a network involving the middle and inferior temporal gyri has been shown to be important in emotional stimuli, and is also inherently connected to attention (Laird et al., 2011). An intriguing hypothesis is that aberrant connectivity should be seen between visual networks to the frontal networks, especially the PFC (Chadick & Gazzaley, 2011), which would support that attention is a necessity in emotional dyscontrol.

Other common resting-state networks include the cingulo-opercular network (sometimes referred to as the core network) linking bilateral insular regions and ACC (Dosenbach et al., 2007), two lateralized parietal-frontal networks that are often associated with attentional processing, and networks that overlap primary sensorimotor and (extra-striate) visual systems (Beckmann, DeLuca, Devlin, & Smith, 2005). In a BD model proposed by Strakowski et al. (2005) there is a dysfunction within subcortical prefrontal networks and associated limbic regions. Furthermore, diminished prefrontal modulation of subcortical and medial temporal structures within the anterior limbic network (e.g. amygdala, anterior striatum, and thalamus) may result in dysregulation of mood in BD (Calhoun et al., 2012).

The task-positive network (TPN), or dorsal attention network (DAN) consists of the DLPFC, inferior parietal cortex (IPC), supplementary motor area (SMA) and extrastriate visual areas. The TPN appears to be associated with cognitive tasks, relating to increased alertness, response preparation and selection (Fox et al., 2005). The TPN seems to be almost perfectly negatively correlated with the DMN, which could reflect a binding mechanism

between the states of attention (Fransson, 2006). It is debated whether the DMN and the TPN should be considered as one network (Fox et al., 2005). It is possible that the cognitive deficits that have been noted in BD-I are associated with aberrant interactions between the TPN and the DMN which could reflect or result in impaired attentional control (Marchetti, Koster, Sonuga-Barke, & De Raedt, 2012)

Another common group of RSNs are lateralized fronto-parietal networks, consisting of the inferior frontal gyrus, medial frontal gyrus, the precuneus/PCC, the inferior parietal and angular gyrus. The fronto-parietal networks have been linked to language (Smith et al., 2009), memory (Damoiseaux et al., 2006), visual processes (De Luca, Beckman, De Stefano, Matthews, & Smith, 2006) and attention (Dosenbach et al., 2007; Fox et al., 2005; Rosazza & Minati, 2011). The right-lateralized fronto-parietal network is shown to be involved in reasoning, attention, inhibition, memory and divided auditory attention tasks (Laird et al., 2011). The attentional and inhibition aspects of this network are relevant to the current study, as attention is necessary for the perception of cognitive and emotional stimuli, while a lack of inhibition can account for the emotional and cognitive dyscontrol in BD.

Resting state fMRI in BD

There are several different methods to approach and analyze resting-state fMRI data (Margulies et al., 2010). They can in general be divided into the categories of seed-based correlation methods and data-driven methods. The former relies on selecting a specific voxel or region as a reference point, whereas the latter requires no specific a-priori hypothesis regarding the spatial localization of the network nodes. More specifically, for the seed-based correlation approach a seed, or predefined ROI is chosen, from which the time-course of the blood-oxygen-level-dependent (BOLD) signal is extracted. Next, the correlations with this time series with other areas of the brain are computed. This can be performed on a ROI by ROI level, or as full-brain analysis, yielding functional connectivity maps reflecting the voxel-wise temporal associations with the specific ROI time series. This is perhaps the simplest and most direct way to study the functional connectivity of the brain, and also provides interpretable results (Fox & Raichle, 2007; Greicius et al., 2003; Rosazza & Minati, 2011).

In a study comparing patients with BD-I to patients with UD, BD-I patients displayed significantly decreased amplitude of low-frequency fluctuations (ALFF) in the left superior parietal lobe and the left posterior insula. BD-I patients also had increased ALFF in the right

dorsal anterior insula compared to UD, suggesting that insular sub-regions may differentiate between BD-I and UD (C. H. Liu, X. Ma, X. Wu, et al., 2012). In another study (Anticevic et al., 2012), global brain connectivity (GBC) restricted to the PFC was used, with a seed placed in the amygdala and PFC. Restricted GBC (rGBC) estimates connectivity at every voxel with every other voxel in a restricted space (M. W. Cole, Anticevic, Repovs, & Barch, 2011; M. W. Cole, Pathak, & Schneider, 2010). BD-I patients exhibited reduced mPFC rGBC, increased amygdala-mPFC connectivity, and reduced connectivity between amygdala and DLPFC, all of which were related to lifetime psychotic symptom severity (Anticevic et al., 2012). The implicated brain regions, including the amygdala and the PFC, are associated with affect regulation, and the aberrant connectivity between these supports the notion of dysfunctional interactions between large-scale brain networks in BD.

Chai et al. (2011) investigated RSFC between the mPFC and a few other regions in 15 healthy controls, 14 BD, and 16 schizophrenia (SZ) patients. Positive correlations between mPFC and insula, and between mPFC and VLPFC were found in the BD group, while the control group exhibited negative correlations (i.e. decoupling). The SZ group showed no significant correlation between any of these regions (Chai et al., 2011). Furthermore, the healthy control group showed significant anticorrelation between DLPFC and mPFC, which was not present in the patient groups. The findings are consistent with the notion of impaired executive functioning in BD shown through task-fMRI (Bertocci et al., 2012), and shows that RSFC between mPFC and insula/VLPFC distinguishes BD from SZ, although the relationship between MRI findings and cognition aren't a direct link.

It is known that amygdala function is modulated by the VPFC/OFC (Strakowski et al., 2012). Following this, it is hypothesized that amygdala dysregulation and VPFC under-activation is an indication of failing network modulation. Indeed, studies have found decreased RSFC between the VPFC and amygdala in BD compared to healthy controls (Chepenik et al., 2010; Foland et al., 2008; Vizueta et al., 2012), and compared to patients with UD (De Almeida et al., 2009). Dickstein and coworkers (2010) used ROI analysis to investigate the left DLPFC, amygdala and accumbens in pediatric BD patients compared to healthy controls. Subsequently, seeds were placed in regions where significant differences in RSFC between the pediatric BD patients and healthy controls were found. The pediatric BD patients had significantly greater negative RSFC between the left DLPFC and the right superior temporal gyrus (STG) compared to healthy controls (Dickstein et al., 2010). This fits with prior studies implicating working-memory functions in BD (Blumberg, Charney, & Krystal, 2002; DelBello, Adler, & Strakowski, 2006). No RSFC differences were found

between the left amygdala or left accumbens seeds (Dickstein et al., 2010). Anand, Li, Wang, Lowe and Dzemidzic (2009) conducted an ALFF study with ROIs including the pregenual ACC (pgACC), dorsomedial thalamus, pallidostriatum and amygdala comparing unmedicated patients with BD (depressed or manic), UD and a matched healthy control group. The BD group showed decreased pgACC connectivity with the left and right dorsomedial thalamus (similar to the UD group), and decreased connectivity with the left and right amygdala and left pallidostriatum. This supports the view of a shared abnormality of corticolimbic RSFC in BD and depression. In spite of this, the small sample size of the BD group (n=12), including the BD-manic and BD-depressed, limits the generalizability of the findings.

Another study using seed-based correlation analysis focusing on the cognitive control network, DMN and affective networks showed an increased connectivity to the same bilateral dorsal medial prefrontal cortex region (dorsal nexus) in all three networks in patients with UD (Sheline, Price, Yan, & Mintun, 2010). All three networks were linked by the dorsal nexus, comprising the bilateral mPFC within the DMN, cognitive control network and an affective network, which are associated with depressive symptomatology (Sheline et al., 2010), and as such, could potentially extend to depressed BD patients. The regional homogeneity (ReHo) approach was used as an index in rs-fMRI to compare aspects of the DMN between 26 BD patients and 26 healthy controls (C. H. Liu, X. Ma, F. Li, et al., 2012). DMN maps were identified using independent component analysis (ICA), the method of which will be discussed further below. Briefly, ReHo measures the local synchronization of spontaneous low-frequency activity of the BOLD response between different brain regions of interest (Wu, Long, Zang, & Wang, 2009; Zang, Jiang, Lu, He, & Tian, 2004). The BD group showed increased ReHo in the left medial frontal gyrus and left inferior parietal lobe compared to the healthy controls, which may be relevant to normal functioning in BD, e.g. in terms of academic performance (Green et al., 2011), and can connect with studies showing overactivity in PFC in BD. These findings can also be related to cognitive-emotional interference, (C. H. Liu, X. Ma, F. Li, et al., 2012) in which the medial fontal gyrus is unable to regulate emotional and cognitive control in BD. Ongur and coworkers (Ongur et al., 2010) compared the DMN in patients with schizophrenia (SZ) and patients with BD. Their results revealed decreased connectivity in the mPFC within the DMN in both groups, possibly reflecting shared difficulties in cognitive-emotion regulation. Interestingly, whereas specific differences between healthy controls and the BD group were found in the parietal cortex, specific differences healthy between controls and SZ were observed in the frontopolar cortex/basal ganglia, suggesting that RSFC is able to differentiate between BD and SZ. In addition, greater

than normal coherence was found within the V1 component in the BD-I patients, possibly reflecting abnormalities in early visual sensory processing.

Calhoun and colleagues (2012) investigated a variety of networks, including subnetworks of the DMN, temporal lobe, and frontal networks using an auditory oddball task. Both the BD and SZ group exhibited similar decreased connectivity in several networks. Notably, alterations in ventromedial and prefrontal DMN was found in the BD group, while changes in the posterior DMN were found in the SZ group. This connects with the hypothesis that depression in BD is induced by the inability to down-regulate it (Sheline et al., 2009). Differences between BD and healthy controls were found in the connectivity between the PCC and a visual component, indicating decreased connectivity between the DMN and the visual system (Calhoun et al., 2012).

In summary, previous studies investigating the effects of BD on RSFC have produced interesting yet some conflicting and inconclusive results. Decreased connectivity has been observed between the amygdala and several brain regions, including the left pallidostriatum (Anand et al., 2009), the DLPFC (Anticevic et al., 2012; Dickstein et al., 2010; Ongur et al., 2010) and the VPFC (e.g. Strakowski et al., 2012). In contrast, increased connectivity has been found between the amygdala and the mPFC (Anticevic et al., 2012). Furthermore, altered connectivity of DMN sub-regions, DLPFC, PCC, cognitive control network and affective network has been found (Ongur et al., 2010). The inconsistent results from previous RSFC studies of BD may be partly explained by heterogeneity in clinical phenotypes and diagnosis across studies and large variability in methodological approaches, and has precluded strong inference about the neurobiological mechanisms underlying BD from RSFC studies in general and for BD-II in particular.

Aims of this study

The main aim of the current study was to characterize functional brain networks in BD-II patients and compare estimates of within and between network connectivity between the patient group and matched healthy controls by utilizing rs-fMRI. The networks of interest were selected based on the studies reviewed above, including the PFC (DLPFC, VLPFC), ACC, amygdala, and visual network, with primary interest on the DMN but also visual networks. DMN abnormality in BD has been found in several studies (Calhoun et al., 2012; C. H. Liu, X. Ma, F. Li, et al., 2012; Ongur et al., 2010). Within-network RSFC differences will be assessed using ICA and dual regression, while between-network differences will be assessed using *FSLNets*. Following the model posited by Townsend and Altshuler (2012),

attention plays a role in the perception of emotional responses. This is followed by attending emotional arousal implicating emotion networks (amygdala, ACC). Finally, the regulation of arousal takes place, implicating the PFC and the DMN. Candidate brain correlates of dysregulated emotion processing and mood in BD-II (connected to mania; Townsend & Altshuler, 2012) has been seen in functional and structural aberrance in ACC (e.g. Hulvershorn et al., 2012; Lyoo et al., 2004), the amygdala (e.g. De Almeida et al., 2010; Dicktein et al., 2005) and the PFC (e.g. Farrow et al., 2005). Cognitive dyscontrol is apparent in BD, including working-memory and decision-making, which has been seen in implicated areas through task-fMRI (and structural studies) revealing aberrance in PFC (including VLPFC and DLPFC; e.g. Vizueta et al., 2012), DLPFC (e.g. Dickstein et al., 2005), and ACC (e.g. Hulvershorn et al., 2012). However, it is important to distinguish between MRI and cognitive measures, and that one doesn't necessarily imply the other.

Based on models of emotional and cognitive processing and dysfunctions in BD-II, we hypothesize that that some form of aberrance will be found in the networks of interest in BD-II patients relative to the healthy controls. As the VLPFC regulates the amygdala (Hariri et al., 2000), the connectivity between these two regions should be decreased. The ACC should show increased connectivity within itself, which could relate to cognitive aspects of BD-II. The DMN encompasses both aspects of cognitive and affective processing, and the highest degree of change should be found within the DMN (especially anterior regions, i.e. PFC and PCC) and between it and other networks. The PCC has rich interconnections to all the suggested substructures, and decreased connectivity should be seen within the DMN, between the DMN subdivisions, as well as with other brain networks. Furthermore, we expected visual networks to display increased connectivity to the amygdala, and increased connectivity with the frontal networks, being a common factor in both cognition and emotion.

Methods and Materials

Sample

Demographic and clinical data are presented in Table 1. Participants provided informed consent in compliance with the Helsinki declaration, and approved by the Regional Ethical Committee of South-Eastern Norway (REK Sør-Øst). Thirty-two (22 females) patients with BD-II between the ages of 18 to 55 (mean [standard deviation (SD)] = 35.47 [7.8] years) and 32 (19 females) matched healthy individuals aged 18 to 55 years (mean = 34.46, SD = 9.43) participated in the study. Patients were identified through psychiatric outpatient clinics in the

Oslo area. The patients were diagnosed with BD-II in accordance with the DSM-IV criteria version 5.0 (Sheehan et al., 1998). The Montgomery Aasberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) and the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) were used to determine mood state at the time of imaging. 26 (38.8 %) patients were taking psychotropic medications ate the time of testing or within the last month prior to testing. This included lithium, antidepressants, antipsychotic agents, benzodiazepines, zolpidem and other mood stabilizers (lamotrigine and valproate). The exclusion criteria for the healthy controls and BD-II patients were: 1) previous or current psychiatric illnesses; 2) below 18 years or above 50 years of age; 3) history of major medical neurological conditions (e.g. epilepsy, migraine, head trauma with loss of consciousness); 4) or any MRI counter indications. About 10 patients that did not complete the study and are not included in any analyses, one because of bad fMRI image quality, while the rest were due to dropout

Table 1

Sample demographics

	Healthy controls (n = 35)	BD-II (n = 32)	*p*
Age (years)	34.46 ± 9.43	35.47 ± 7.76	.635
Education			
Gender(male:female)	16:19	10:22	.231
MADRS	1.26 ± 1.65	9.91 ± 7.38	< .001
YMRS	0.314 ± 0.676	2.355 ± 2.025	< .001
Hypomanic episode, n (%)	0	1 (1.5)	
Depressive episode, n (%)	0	12 (17.9)	
No. of people with psych drug 1 month prior, n (%)	0	26 (38.8)	

Neuropsychology

All participants were tested using modified versions of the Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996) and the Brief Visuospatial Memory Test (BVMT-R; Benedict, 1997)**.** The BVMT consists of six figures and three trials but was extended to 12 figures and five trials. Similarly, the RAVLT consists of 5 trials with 15 nonsemantically or phonetically related words, which was extended to 20 words, in line with Pereira et al. (2007). This was done to increase variability in memory performance among the healthy controls. The interval

between testing was around but did not exceed two hours, where the participants were assessed on delayed recall and recognition for both the BVMT-R and RAVLT.

MRI acquisition and analyses

MR data was collected with a 3 Tesla Philips Achieva Scanner (Philips Healthcare, Eindhoven, the Netherlands) using an eight-channel SENSE head coil at the Intervention Centre, Oslo University Hospital. Resting state blood-oxygen-level-dependent fMRI data was collected for each subject with a T2*-weighted single-shot gradient echo EPI sequence with the following parameters: TR/TE/FA = 2.500ms/30ms/80°; voxel size, 2.65 × 2.65 × 3.00 mm; 45 axial slices, 200 volumes; scan time ≈ 8 min. During the whole-brain functional resting-state acquisition the participants were instructed to have their eyes closed, stay awake and not to think of anything in particular. Scanner noise and subject notion was reduced by using cushions and headphones. A T1-weighted 3D turbo field echo (TFE) sequence with the following pulse sequence parameters was obtained for registration purposes: repetition time (TR)/echo time (TE)/flip angle (FA) = 8.5ms/2.3 ms/7°; voxel size = 1.0 × 1.0 × 1.0 mm, 220 sagittal slices, scan time = 7 min 40 sec.

MRI analysis

Pre-processing of structural data was done using FreeSurfer 5.1.0 (http://surfer.nmr.mgh.harvard.edu/), including removal of non-brain tissue (Jenkinson, Pechaud and Smith, 2005; Smith, 2012). The T1-weighted data was only used for registration purposes (see below) in the present study, and a complete description of the processing stream in Freesurfer is beyond the scope of this thesis. Briefly, we used the automatic brain segmentation as a mask in order to create a precise brain extraction for use in the registration algorithms.

For fMRI, the first five volumes were discarded on the scanner to let the magnet reach equilibrium due to progressive saturation. Functional data was pre-processed using FSL 5.0.1 (http://fsl.fmrib.ox.ac.uk/fsl), including motion correction and skull stripping. We used TOPUP (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TOPUP) for spatial unwarping. Briefly, each fMRI volume was spatially unwarped using two unique (dual) spin echo EPI volumes, which estimates the susceptibility-induced off-resonance field (Smith et al., 2004). Conventional processing of the FMRI data included spatial smoothing using a Gaussian kernel of FWHM of 5mm, and high-pass temporal filtering equivalent to 120s. FMRIB's Nonlinear Image Registration tool (FNIRT) was used to register the participant's fMRI volumes to standard

space (MNI-152) with the T1-weighted volume as an intermediate. Boundary based registration (BBR; Greve & Fischl, 2009) was used to refine the registrations.

Independent component analysis

In the current study we utilize the ICA approach, a multivariate technique based on blind source separation providing unbiased estimates of spatiotemporal RSNs across all included subjects (D. M. Cole, Smith, & Beckmann, 2010). The main difference between seed-based approaches and ICA is that the latter requires no a-priori hypothesis or seed selection, and reliably extracts functional RSNs based on covariance ICA creates spatial maps from the BOLD time series (Damoiseaux et al., 2006; Margulies et al., 2010).

Group-ICA was performed on all of the subjects using FSL's Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC; Jenkinson, Beckman, Behrens, Woolrich, & Smith, 2012), yielding a set of common ICs across all subjects. Currently, there is no consensus on the optimal model order/dimensionality (number of components). A few studies have approximated that a model order of 70 conveys the largest between group difference (Elseoud et al., 2011; Kiviniemi et al., 2009), and higher model orders (De Martino et al., 2007; McKeown, Varadarajan, Huettel, & McCarthy, 2002) may provide the most functionally differentiated brain segmentation (Kiviniemi et al., 2009). High model orders can substantially decrease the stability of the IC estimates (Y. Li, Adali, & Calhoun, 2007). In the current study, MELODIC was set to estimate 80 components. In an additional run, MELODIC automatically estimated the number of independent components using a Laplacian approximation (Beckmann, Mackay, Filippini, & Smith, 2009; http://fsl.fmrib.ox.ac.uk/fsl). Thirty-nine components identified as artefacts were excluded (see Figure 9 in the Appendix), leaving a total of 41 components (see Figure 8 in the Appendix).

Dual Regression

The set of spatial maps from the group-ICA was used to generate subject-specific versions of the spatial maps, and associated time series, using dual regression (Beckmann, Mackay, Filippini, & Smith, 2009; Filippini et al., 2009). First, dual-regression identifies subject-specific temporal dynamics and associated spatial maps, where the group-ICA spatial maps are set in a linear model (spatial regression) against the individual fMRI datasets. This results in a set of subject-specific timeseries, one per group-level spatial map. Next, those timeseries

are regressed (as temporal regressors, again in a multiple regression) into the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map.

Subject motion

Several steps were taken to minimize the impact of subject motion on the estimates RSFC measures. First, all functional series were affine realigned to the middle volume, and the estimated extended motion parameters were used as additional regressors in the second stage of dual regression, using *mp_diffpow.sh* (distributed with FSL). Here, the first six columns represent the standard motion parameters, being three translations (right, forward and up) and rotations in radians (pitch, roll and yaw). The next six columns are the square of these motion parameters, the next 6 are the temporal difference of the motion parameters, and the last six are the square of the differenced value. This is useful for accounting for 'spin history' effects and noise covered by motion correction. The second part involved the identification and modeling of volumes with excess movement (*fsl_motion_outliers*) or so called "spikes", the information of which is also added into the second stage of dual regression allowing the volumes with heavy motion to be modeled out. These two additions are unlikely to remove all effects of the subject motion artefacts, but should in theory have a substantial impact.

Statistical analysis

Demographic and neuropsychological variables

Differences in sex distribution between diagnostic groups were tested using chi-square test. Differences in age and neuropsychological performance were tested using multiple linear regressions including sex and age (for the cognitive measures) as covariates using PASW statistics 18.0 (SPSS) .

Within-network connectivity

The subject-specific component spatial maps were concatenated across subjects and submitted to voxel-wise between-subject analysis testing for effects of diagnosis on functional connectivity using FSL's *randomise* tool, allowing for non-parametric permutation based inference (Nichols & Holmes, 2002). FSL's GLM was used to set up different contrasts to test for main effects of diagnosis (BP-II > Controls, Controls > BP-II) including age and sex as covariates. For each contrast, 5000 permutations were run and Threshold-free cluster enhancement (TFCE; Smith & Nicols, 2009) was used for statistical inference to validate the likelihood of extended areas of signal, by using information from neighboring voxels. This is

more sensitive than voxel-wise thresholding, and does not require setting an arbitrary initial cluster-forming threshold such as conventional cluster-based thresholding (Smith & Nicols, 2009). As a result, TFCE gives in general better sensitivity than other methods (Smith & Nicols, 2009). Nominal alpha was set to $p < .05$, corrected for multiple comparisons across space using permutation testing and TFCE.

Between-network connectivity

As of yet, few studies have investigated the temporal relationships between various RSNs, and even fewer have investigated the total RSN structure. This can be achieved by performing hierarchical clustering of the correlation matrix of the BOLD time courses of each component from dual regression (stage 1). The correlation matrix is a summary of the temporal relationships between all components (Joyce, Hayasaka, & Laurienti, 2013). Each component represents a node (vertex), represented by rows and columns, and connected to each other by links (edges) which are represented by the matrix entries of temporal correlations. The relationship between these components represents patterns of causal and non-causal interactions (Rubinov & Sporns, 2010). In the final stage, components are clustered together according to how correlated they are with each other. This happens on various levels, and also serves to validate connections between brain networks (e.g. DMN sub-regions should ideally be clustered together). There are several tenets of network level analyses. One is that it allows insights into structural-functional connectivity relationships in individual subjects (e.g. Honey et al., 2009). In the cases of brain disorders, one can potentially detect abnormalities across populations of network connectivity (Bassett & Bullmore, 2009). In this study, we investigated the effects of diagnosis on the functional connectivity between the DMN, frontal, visual networks and amygdala in relation to each other and with other networks.

While the order of nodes has no effect on computation of network measures, it can be important for the clustering part. Importantly, nodes should represent brain regions that can be separated from others, the criteria of which the components from ICA fulfill. Incidentally, it may be less meaningful to lump larger components together (Rubinov & Sporns, 2010). This was one motivation for running ICA with a higher model order, so that the relationship between sub regions (e.g. of the DMN) to all other brain regions could be elucidated.

Network modeling was carried out using a set of MATLAB (2010) scripts distributed with FSL (Smith et al., 2011) . The main input is N timecourses (from dual regression stage 1) from all 67 subjects. The group-level spatial maps from MELODIC group-ICA are used, with

one map per node. Using the time courses, a network matrix is computed for each subject, which is an NxN matrix of correlation coefficients. A clustering of nodes is created based on the full correlations of each node (converted to t-values). This clustering is in a hierarchy on several levels, such that nodes most correlated with each other are grouped together on the bottom level, with the least correlated networks in a larger group on the highest level. A plausible assumption would be that visual networks are grouped together in one cluster, and motor networks are grouped together in a smaller cluster. The edges on the network matrix represent the temporal correlation between two nodes**.** The diagonal in the network matrix (top left to bottom right) represents autocorrelation (i.e. a node correlated with itself). We calculated both the full and the partial correlations between all components, and visualize both estimates as color-coded matrices where edges below the diagonal represent full correlation, while the edges above the diagonal represent partial correlation. In this case, the partial correlation measures the degree of association between two brain networks while controlling the effects of all the other brain networks.

We carried out several multiple linear regression analyses with diagnosis, sex and age as independent variables and each element in the correlation matrix of the component time series as dependent variable in order to test the main effects of diagnosis on each correlation pair using the *glmfit* function in MATLAB. In order to account for the inflated probability of Type I errors due to the large number of tests, the results were corrected using Bonferroni correction (Genovese, Lazar, & Nichols, 2002).

Brain network clusters

In addition to the quantitative analysis, we have decided to do a qualitative (visual) inspection, whereby we compare the clustering hierarchy of the BD-II patients to the healthy controls, and to the whole dataset. In particular, we will look at whether certain components (e.g. sensory) are clustered in the same gross location, how many lower level clusters there are, and the number of hierarchical levels.

Results

Neuropsychological tests

Table 1 summarizes the demographic and neuropsychological measures for each diagnostic group. Age (t = -0.477, p = .635), and sex distribution was not significantly different between groups (χ^2 = 1.473, df = 1, p = .225). We observed a significant difference in learning rate between HC and BD-II (t = -2.849, p = .006) for BVMT-R, indicating decreased learning performance in the patient group (mean [*SD*]: 11.72 [4.53248]) compared to healthy controls (mean [*SD*]: 14.2581 [3.17246]) with a 'medium' effect size (Cohen's d = 0.46529). In contrast, no group differences were found in BVMT learning (t = -1.833, p = .073), total recognition (t = -1.763, p = .084), correct hits on recognition (t = -1.717, p = .092) and false positive errors on recognition (t = 1.912, p = .061). Except for a significantly decreased performance on RAVLT delayed recall in patients with BD-II (t = -2.122, p = .039) with a medium effect size (Cohen's d = 0.465), no other group differences on RAVLT were found.

Table 2

Overview of scores on BVMT-R and RAVLT

	Healthy Control group (n = 31)	BD-II group (n = 25)	*t*	*p*
Age	35.10 ± 9.67	34.96 ± 8.22	-0.477	0.635
Gender(male:female)	15:16	10:15	-0.481	0.231
BVMT-R				
Learning: Sum of Trials 1-5	65.48 ± 17.51	57.08 ± 23.19	-1.833	0.073
Total recognition	14.21 ± 2.59	13.06 ± 2.78	-1.763	0.084
Delayed recall	15.06 ± 3.33	13.64 ± 4.00	-1.789	0.800
Correct hits on recognition	11.68 ± 0.65	11.32 ± 0.85	-1.717	0.092
False positive errors on recognition	0.35 ± 0.84	0.84 ± 1.21	1.912	0.061
Learning score (rate) (T5 / T1)	14.26 ± 3.17	11.72 ± 4.53	-2.849	0.006
RAVLT				
Learning: Sum of Trials 1-5	71.06 ± 12.95	65.28 ± 13.90	-1.763	0.084
Total recognition	13.10 ± 3.50	11.42 ± 4.64	-1.833	0.073
Delayed recall	18.35 ± 4.84	15.72 ± 6.36	-2.122	0.039
Correct hits on recognition	19.19 ± 1.05	19.16 ± 1.49	-0.114	0.910
False positive errors on recognition	1.10 ± 1.68	1.68 ± 2.41	1.162	0.251
Learning score (rate) (T5 / T1)	8.26 ± 2.78	8.12 ± 2.91	-0.267	0.791

Note. Data from the neuropsychological tests was missing for 11 participants (5 healthy controls, 7 BD-II patients).

ICA

A total of 40 and 80 components were automatically extracted with MELODIC from the group ICA analyses. Automatic estimations of model order extracted less than 20 components in the current dataset, which was deemed too sparse for network modeling. Furthermore, about half of the components tend to be artefactual (see Appendix, Figure 9), so the model order of 80 was chosen.

Several components were chosen for further analysis, many of which were selected based on visual comparisons with previously published components (Damoiseaux et al., 2006; S. M. Smith et al., 2009; Veer et al., 2011). Four components were identified as comprising the DMN (IC00, IC08, IC09 and IC 50; see Figure 1). Two components (IC02 and IC03) comprising the visual system were also identified and chosen for further analysis due to considerable spatial overlap with regards to the posterior regions of the DMN, and being connected to attention. The TPN (IC15 and IC20) was also analyzed, as decoupling between it and the DMN could relate to inhibition of (cognitive) task performance. Various frontal networks were analyzed (IC26, IC35, IC26) that spatially overlap with the PFC (i.e. DLPFC, VLPFC), as well as the right frontoparietal network (IC01). Finally, IC29 was chosen because it encompasses the medial temporal lobes (i.e. amygdala and hippocampus).

Within-network connectivity

Permutation yielded no significant results for TFCE thresholding for the DMN, TPN, amygdala or frontal components at $p < 0.05$ for the BP-II > Control or Control > BP-II contrasts. This suggests that there is no difference in connectivity between healthy controls and BD-II patients within these networks.

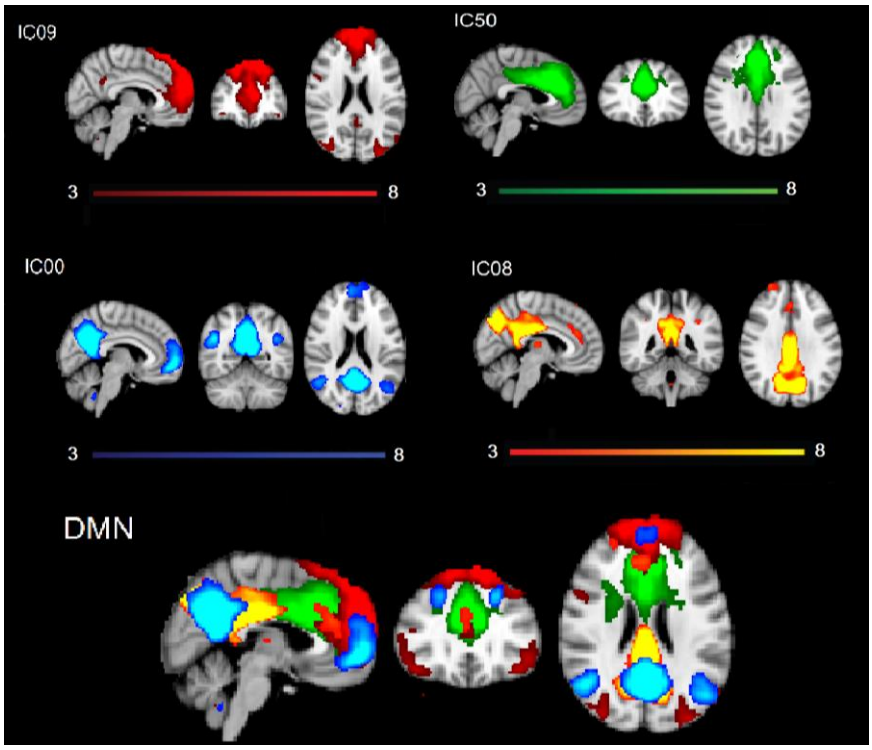

Figure 1. Independent components IC00 (precuneus, midline frontal pole), IC08 (ACC, PCC, angular gyrus), IC09 (frontal pole, superior frontal gyrus) and IC50 (cingulate gyrus, paracingulate gyrus) that are subcomponents of the DMN. These components are shown together at the bottom row.

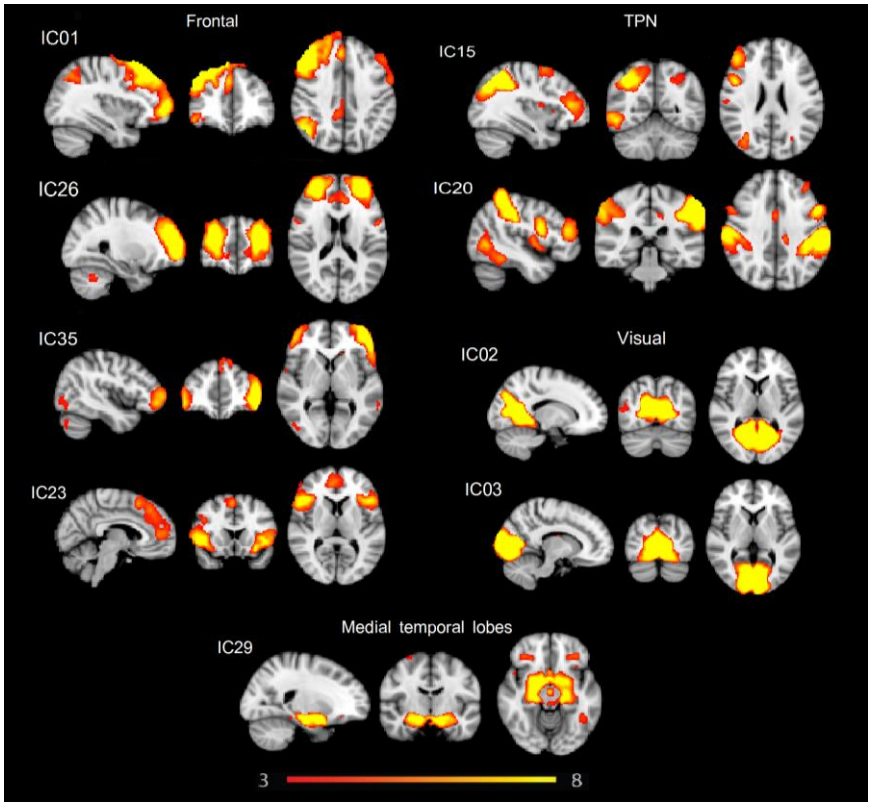

Figure 2. Other selected ICs. The left panel consists of frontal cortex components, IC26 (frontal pole/rostral middle frontal), IC01 (right fronto-parietal), IC35 (middle frontal gyrus) and IC23 (inferior frontal gyrus and precentral gyrus). The right includes two TPN components, IC15 and IC20, and two visual components, IC02 (intracalcarine cortex) and IC03 (occipital pole). The bottom, IC29 (medial temporal lobes) overlaps with the amygdala and to some degree, the hippocampus.

Between-network connectivity

Thresholds were set at $p < .05$ for between-group connectivity after correcting for multiple comparisons by Bonferroni correction. None of the edges were significant after Bonferroni testing, and as such should be interpreted with caution. However, since conservative Bonferroni correction is likely to produce several false negatives (Type II errors), we think it is relevant to describe trend effects that differentiate BD-II patients from healthy controls. As a result, the threshold was set to $t > |2.35|$ to illustrate some of the changes (see Figure 5). Only results of particular interest will be noted, the rest can be seen in Table 3 (with an explanation of different values).

IC16 (precentral gyrus; primary motor cortex) and IC02 (visual) display decreased connectivity ($t_{difference} = -3.46$, $p = .001$) in BD-II patients ($t_{correlation} = 0.58$) compared to healthy controls ($t_{correlation} = 2.65$). IC00 (precuneus, anterior DMN) and IC29 (amygdala) showed increased connectivity ($t_{difference} = 2.94$, $p = .0046$) in BD-II patients ($t_{correlation} = 0.0982$) compared to healthy controls ($t_{correlation} = -0.71$). IC13 (middle and inferior frontal gyrus) showed decreased connectivity with IC27 (Heschl's gyrus; $t_{difference} = -3.38$, $p = .0012$) in BD-II ($t_{correlation} = -1.3$) compared to healthy controls ($t_{correlation} = -0.12$), the second closest to reaching statistical significance after multiple correction. IC18 (superior parietal lobule) shows change in connectivity to 5 other networks; possibly indicating "hub" properties (see Figure 6). It shows increased connectivity with IC15 (TPN; $t_{difference} = 0.8326$, $p = .009$) in BD-II ($t_{correlation} = 0.83$) compared to healthy controls ($t_{correlation} = -0.32$) decreased connectivity with IC03 (visual; $t_{difference} = -2.39$, $p = .0199$) in BD-II patients ($t_{correlation} = 0.69$) compared to healthy controls ($t_{correlation} = 1.96$), decreased connectivity with IC35 (middle frontal gyrus; $t_{difference} = -2.39$, $p = .0201$) in BD-II patients ($t_{correlation} = -0.50$) compared to healthy controls ($t_{correlation} = 0.80$), decreased connectivity with IC30 (visual component; $t_{difference} = -2.76$, $p = .0076$) in BD-II patients($t_{correlation} = 0.39$) compared to healthy controls ($t_{correlation} = 1.89$), and decreased connectivity with IC19 (visual component; $t_{difference} = -2.59$, $p = .0119$) in BD-II patients ($t_{correlation} = 1.91$) compared to healthy controls ($t_{correlation} = 3.60$). Lastly, IC32 (lateral occipital cortex) shows increased connectivity with IC03 ($t_{difference} = 2.92$, $p = .0049$) in BD-II patients ($t_{correlation} = 1.02$) compared to healthy controls ($t_{correlation} = -0.21$) and increased connectivity with IC09 (frontal DMN; $t_{difference} = 2.38$, $p = .0211$) in BD-II patients ($t_{correlation} = -1.63$) compared to healthy controls ($t_{correlation} = -1.99$).

Table 3

Between-network connectivity

ICA component	ICA component	Mean connectivity in BD-II patients ($t_{correlation}$)	Mean connectivity in healthy controls ($t_{correlation}$)	Mean connectivity across groups ($t_{correlation}$)	$t_{difference}$	*p*
29	0	0.09 ± 1.47	-0.71 ± 1.48	-0.33 ± 1.52	2.94	.0046
16	2	0.58 ± 1.72	2.65 ± 2.12	1.67 ± 2.19	-3.46	.0010 [a]
18	3	0.69 ± 1.64	1.96 ± 1.97	1.36 ± 1.92	-2.39	.0199
32	3	1.02 ± 1.96	-0.21 ± 1.75	0.38 ± 1.94	2.92	.0049
27	4	-2.80 ± 1.81	-1.69 ± 2.19	-2.22 ± 2.08	-2.40	.0196
22	6	1.64 ± 2.11	0.20 ± 2.40	0.89 ± 2.36	2.38	.0205
34	6	0.83 ± 1.53	-0.20 ± 1.12	0.29 ± 1.42	3.24	.0019
32	9	-1.63 ± 1.82	-1.99 ± 1.64	-1.82 ± 1.72	2.37	.0211
25	10	-1.06 ± 1.86	-0.16 ± 1.26	-0.58 ± 1.63	-2.93	.0048
34	10	5.71 ± 1.40	4.60 ± 1.55	5.14 ± 1.57	2.87	.0056
27	13	-1.30 ± 2.03	-0.12 ± 1.73	-0.69 ± 1.96	-3.38	.0012 [b]
52	13	-1.55 ± 1.55	-2.80 ± 1.32	-2.21 ± 1.56	2.88	.0054
18	15	0.83 ± 1.80	-0.32 ± 1.81	0.23 ± 1.88	2.70	.0090
24	15	-0.87 ± 1.76	0.13 ± 1.21	-0.35 ± 1.57	-2.42	.0184
19	18	1.91 ± 2.29	3.60 ± 2.19	2.80 ± 2.38	-2.59	.0119
30	18	0.39 ± 1.73	1.89 ± 2.23	1.17 ± 2.16	-2.76	.0076
35	18	-0.50 ± 1.80	0.80 ± 1.94	0.18 ± 1.97	-2.39	.0201
23	22	-2.97 ± 1.93	-4.14 ± 1.45	-3.58 ± 1.78	3.13	.0027
52	35	-1.45 ± 1.73	-2.70 ± 1.42	-2.10 ± 1.69	3.28	.0017
42	41	-0.47 ± 1.43	-1.58 ± 1.70	-1.05 ± 1.66	2.36	.0215

Notes. The correlation between two nodes ($t > |2.35|$) in BD-II patients, healthy controls, and across groups with the associated (uncorrected and corrected) p-stats and t-stats. The $p > 0.05$ threshold becomes $p > 0.00006098$ after Bonferroni correction. The connectivity measures are t values that have been converted from the Pearson product moment correlation coefficient, and reflect the strength and direction of the correlation. A graphical depiction of the connectivity between brain networks can be seen in Figure 5 and Figure 6, with the corresponding networks.

[a] The highest p-value, i.e. the closest to reaching statistical significance.

[b] The second highest p-value, i.e. the second closest to reaching statistical significance.

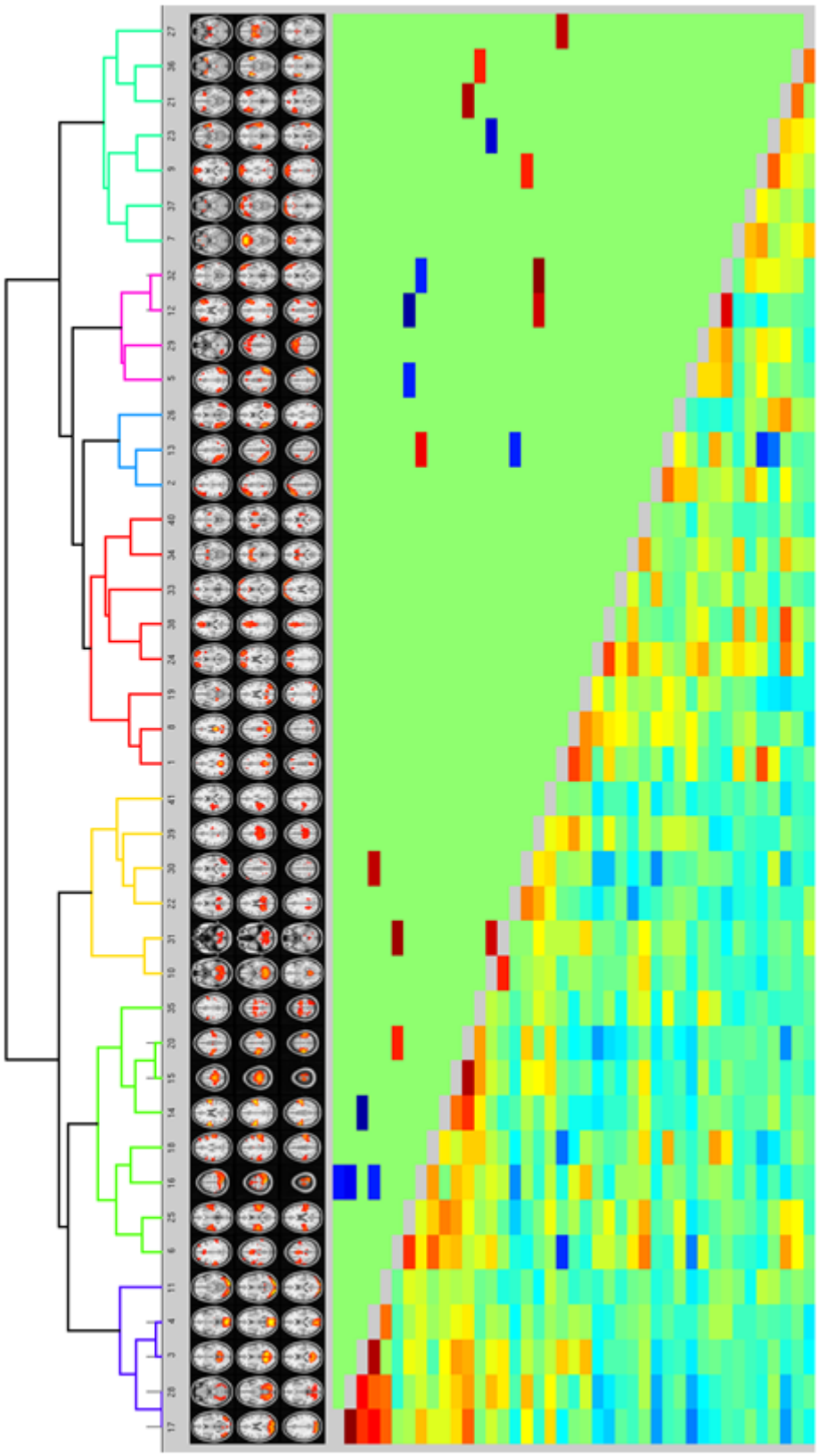

Figure 5. A hierarchial network plot of all the included brain components from ICA. Each component is denoted by one column (i.e. three brain images per component). The coloured matrix below the "grey" diagonal (autocorrelation) displays the full correlation of time-series between components. Each "rectangle" is the correlation between two components across groups. Dark red indicates a high positive correlation, light green indicates 0 correlation, and dark blue represents high negative correlation. The matrix above the grey diagonal is displaying the (statistically) uncorrected effect of diagnosis on the (full) correlation between brain networks ($t > |2.35|$). Dark red indicates higher correlation between the two components in BD-II patients, dark blue indicates higher correlation between the two components in healthy controls, while light green indicates no ddifference. Importantly, none of the effects survided stringent Bonferroni correction.

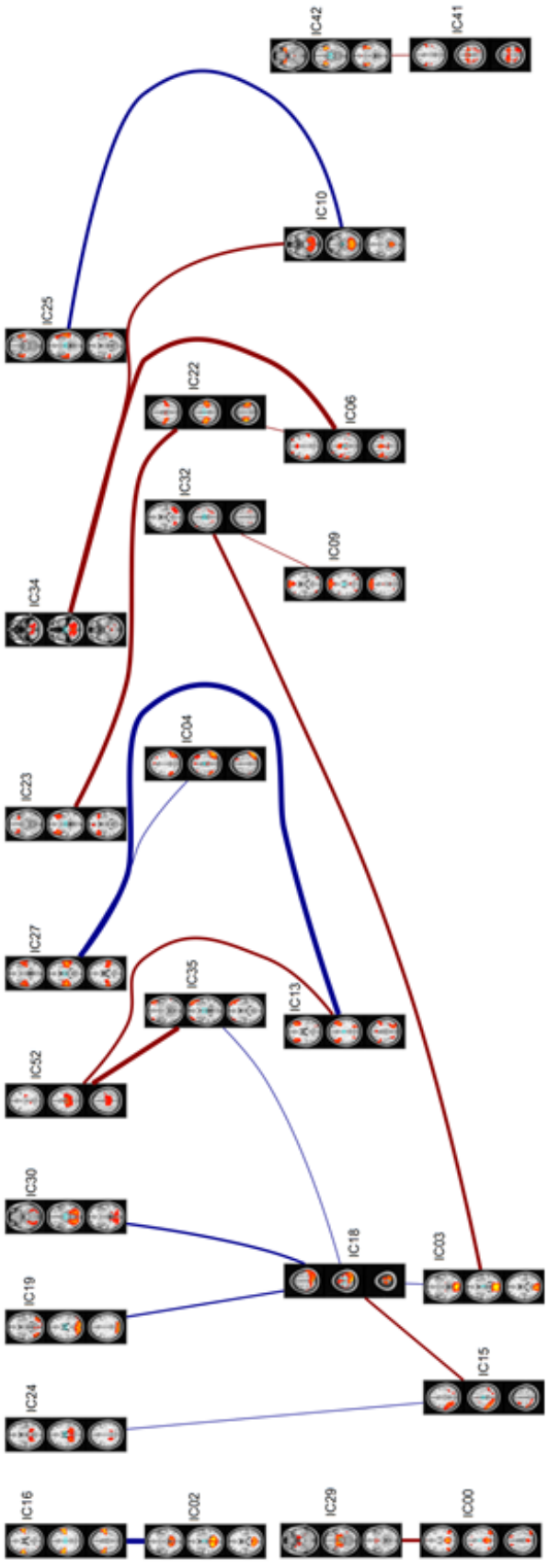

Figure 6. A network plot showing the (uncorrected) effect of diagnosis (BD-II) on the correlation between brain networks ($t > |2.35|$). Blue lines indicate components that are more correlated with each other in the healthy controls. Red lines indicate components that are more correlated with each other in the BD-II patients. The thickness of the lines represents the magnitude of the difference in correlation between groups. This plot is an alternative visualization of the effects presented in Figure 5.

IC16 – precentral gyrus (primary motor cortex); IC18 – superior parietal lobe (spatial orientation); IC27 - Heschl's gyrus (primary auditory cortex); IC32 – lateral occipital cortex (object recognition); IC34 – cerebellar component; IC25 – temporal pole-STG-MTG-angular gyrus; IC22 – post central gyrus (primary somatosensory cortex); IC6 – operculum cortex (supplementary motor cortex); IC13 – middle and inferior frontal gyrus; IC04 – angular gyrus; IC10 – cerebellar component

Brain network clusters

Figure 7 shows the hierarchical clustering of brain networks, for the BD-II patients, the healthy controls, and the whole dataset. The same visual and auditory networks are clustered together on the very left of the network map, although in different orders. Two of the DMN subcomponents (Numbers 1 and 8 in Figure 7.) are in the same cluster at the lowest level, and next to each other on all three clusters. Part of the frontal DMN (Number 38, Figure 6) is in the same cluster as the two aforementioned DMN subcomponents in the network exclusively for healthy controls and the network for all participants. In spite of this, they are in the same secondary level cluster, all on the "right side" of the "network" map.

Overall, the three clustering hierarchies are quite similar. All three have two large groups/levels of clusters. As expected, the sensory (including visual networks) and motor networks are lumped together in a cluster in all three "network maps", being highly correlated with each other.

Interestingly, the cluster that contains all participants is visually more similar to the cluster exclusive for the BD-II patients than the healthy controls, having the same amount of coloured (lower level) clusters. The first three clusters in the BD-II network and the "all participants" network are almost exactly the same, with just a slight difference in order of components. The healthy control "network" has one less lower level cluster than the two other "networks".

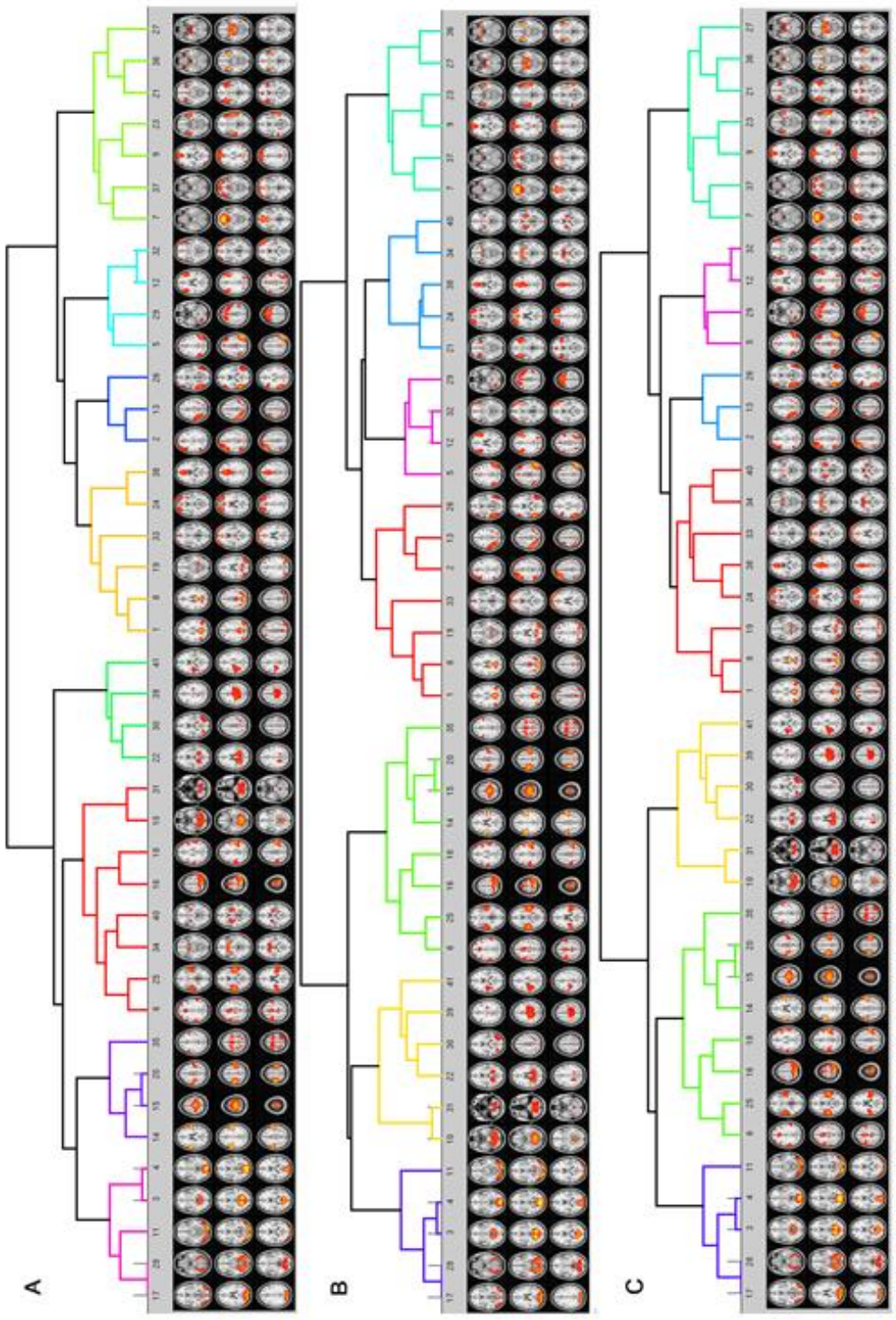

Figure 7. These images show the clustering hierarchy of brain networks, based on the full correlations of time courses between components, with the top panel (A) representing healthy controls, the middle panel (B) representing patients with BD-II, and the bottom panel (C) representing both patients with BD-II and healthy controls. Panel (C) can also be seen in Figure 5.

Discussion

Using a combination of ICA and dual-regression, followed by network modeling, we have demonstrated that BD-II is very similar to healthy controls, both in terms of performance on neuropsychological tests, and functional brain networks. Specifically, we found no (statistically) significant change in between-network functional connectivity within the DMN, TPN, frontal networks or the amygdala (medial temporal lobes), as well as between these and other networks. The implications of these findings will be discussed below

Neuropsychology

We observed decreased test performance in BD-II compared with healthy controls on BVMT-R, which is assumed to be sensitive to learning performance. This indicates that there is impairment localized to learning of verbal material. Additionally, a significant difference in delayed recall was found in the RAVLT, but not any of the other measures. In contrast to the BVMT-R, this indicates impairment in the extraction of memory related to non-verbal material. It is important to note that the total recognition (or total learning) of items in both of these tests were similar for both of the groups, indicating that attention is not (significantly) impaired. This is in contrast with studies of BD-I, where impairment is seen on several measures across cognitive tasks (Torrent et al., 2006). The results from the RAVLT contrast the results on the CVLT for BD-II patients in the study by Torrent et al. (2006), where semantic verbal fluency and verbal learning and memory was most affected. Still, their results overall indicate that cognitive abilities was only slightly impaired in BD-II patients and supports the notion of high functioning in BD-II patients (Green et al., 2011). This does not fit in the model by Strakowski et al. (2012), as attention does not seem to be impaired, which is the initial requirement of the model. A review by McCrea (2008) suggests that the BD spectrum disorders are not necessarily characterized by verbal or visual memory. One can infer that this is particularly true in terms of BD-II, being a less “severe” disorder than BD-I. In addition to neuroimaging, future studies should use neuropsychological tests more sensitive to apparent BD cognitive deficits, such as the WSCT, TMT and Stroop interference tasks (Torrent et al., 2006), and possible also implement sensitive experimental cognitive paradigms which are assumed to be more sensitive to specific cognitive sub-components.

Within-network connectivity

No changes in connectivity were found within the TPN, frontal networks, amygdala, or visual networks which indicates functional coherence within these brain regions. Coherence in frontal network indicates perseverance of emotional and cognitive control.

No difference was found within any of the DMN-subregions, where Calhoun (2012) showed alterations in ventromedial and prefrontal DMN in BD-I, or decrease in connectivity in the mPFC within the DMN (Ongur et al., 2010). However, the latter could be explained by the oddball auditory task they were doing, a stark contrast to no paradigm (i.e. rest), which was used in the present study.

With the exception of two structural neuroimaging studies previously mentioned (Elvsåshagen et al., 2013; Vizueta et al., 2012), this is one of the few studies to exclusively use BD-II patients in a functional neuroimaging context, and the first to use it investigating RSNs. Likewise, with the exception of C. H. Liu, X. Ma, F. Li et al. (2012) it is currently one of the few studies to implement ICA in any stage of the analysis procedure. It is prudent that one compares this to future studies using a similar methodology, to correctly ascertain if in fact there is no difference between BD-II patients and healthy controls within brain networks.

Between-network connectivity

The similarity in network hierarchy indicated no significant difference between BD-II patients and healthy controls on a brain network level. This suggests that there is a coherence of overall brain network hierarchy in BD-II patients, and that the relationships between these brain networks function close to "normal." This is corroborated by the striking similarity in the clustering hierarchy of brain networks in BD-II patients and healthy controls, which points towards similar functional interactions between the networks across the two groups.

Still, some trend effects indicating non-significant differences in temporal correlations between specific network nodes were observed. Again, even though the results are not statistically significant, and therefore should be interpreted with caution, they can hint towards slight differences.

Two of the networks studied, IC00 (part of DMN) and IC29 (amygdala) exhibited increased connectivity in the BD-II group. Importantly, the networks are on average slightly positively correlated in BD-II (T-BDII = 0.0982) while they are slightly negatively correlated in healthy controls (T-CON = -0.7128). Although previous studies have not shown dysfunctional connectivity between the DMN and amygdala, IC00 also contains the midline frontal pole (PFC). The PFC has been shown to modulate the amygdala (C. H. Liu, X. Ma, F.

Li, et al., 2012; Strakowski et al., 2012), i.e. one would expect close interactions between amygdala and PFC activation. The correlation between these nodes have been found to be related to psychotic symptom severity in one study (Anticevic et al., 2012), although reduced connectivity was found. The fact that the opposite occurs in the BD-II patients is an indication of emotional dyscontrol, although the connectivity within these networks are unperturbed. This could also provide support that specific parts of the DMN have a secondary (specific) role (Buckner et al., 2008).

None of the other DMN-subregions showed aberrant connectivity with any other networks. Previous results have shown aberrant connectivity with the mPFC (Sheline et al., 2010), although that was related to symptom severity of depression. Notably, none of the PFC components acted as a "hub" for aberrant connectivity. This ties in with lack of differences within DMN subnetworks found in this study.

No (increase) difference in connectivity was found between mPFC and VLPFC, in contrast to Chai et al., (2011). Incidentally, no difference was found in the connectivity between frontal networks (i.e. the DLPFC) and medial temporal lobes (i.e. amygdala). This fits with our behavioural results where there was no impairment in working-memory on the RAVLT or BVMT-R, going against other studies (Blumberg et al., 2002; DelBello et al., 2006), although they were looking at the whole BD spectrum, primarily BD-I.

Decreased connectivity was found between a frontal component and an auditory component. Parts of the frontal lobe, including the DLPFC, have shown to be important in integrating sensory information (Fuster, 2002) and important for attention (Büchel & Friston, 1997), possibly indicating decreased integration and attention in BD-II patients. This can be connected to the decreased connectivity between several auditory and visual components in patients with BD-II in this study. As the lateral occipital cortex plays a role in object recognition (Grill-Spector, Kourtzi, & Kanwihser, 2001), increase in connectivity between IC32 and the frontal DMN (IC09) could be related to mind-wandering involving object-recognition. However, the connectivity between them is still negative (see Table 3), so it is only a minor difference.

Increased connectivity between a cerebellar and a frontal (IC06) component can be explained by the various inputs the cerebellum receives from frontal lobe structures including the PFC, DLPFC, medial frontal gyrus, and VLPC (Allen et al., 2005), regions implicated in BD. In fact, one study indicates that cerebellar volume atrophy occurs later in life in the BD-patients suffering from multiple affective episodes (DelBello, Strakowski, Zimmerman, Sax, & Hawkins, 1999), indicating that it is part of the pathophysiology of BD.

A superior parietal component (IC18) showed aberrant connectivity with five other networks in BD-II patients. This indicates that the superior parietal lobule may act like a hub in the pathophysiological processes in BDII. In a lesion study (Koenigs, Barbey, Postle, & Grafman, 2009), the superior parietal cortex has been linked to the manipulation of information in working-memory. As a result, decreased connectivity with the visual components (IC03, IC19 and IC30) could suggest issues with the encoding and/or retrieval of memory involving visual manipulation (i.e. remembering locations in a setting). Increased connectivity with the TPN (IC15) and middle frontal gyrus (IC35) could suggest faulty manipulation of memory during tasks and/or requiring executive functioning.

The above points on differences in the BD-II group are speculative, and we emphasize that the lack of statistical differences in term of aberrant connectivity between networks related to attention, emotion and cognition suggest that there is no severe deficits in terms of emotion regulation or cognition control. These findings are in accord with the high functioning and the general lack of differences on neuropsychological test performance. Future studies should investigate the connectivity between the DMN and the amygdala, as both structures and their integration are implicated in several models of BD (e.g. Sheline et al., 2009).

Limitations and future considerations

There are a couple of variables that were not modeled into the within-networks and between-networks connectivity. One of them was medication history, which included lithium, antidepressants, antipsychotic agents, benzodiazepines, zolpidem and other mood stabilizers (lamotrigine and valproate). Twenty-six (38.8%) of the BD-II patients in this study were taking psychotropic drugs one month prior to the study, and we cannot rule out that this has influenced our results. Nonetheless, an extensive review article (Hafeman et al., 2012) suggests that psychotropic medication (including but not limited to anticonvulsants, atypical anti-psychotics, lithium, and anti-depressants) typically taken by people diagnosed with BD have only small effects on functional neuroimaging parameters, although future studies should not take this for granted. Another was the results from the RAVLT and BVMT-R, which does not effectively distinguish BD-II patients from healthy controls and as previously mentioned, other neuropsychological tests may be better suited. Lastly, the depression and hypomanic states as revealed by MADRS and YMRS respectively, as well as the episodes the patients were experiencing during the time of scanning were also not modeled in. In general, the reason why they were not taken into account for was that we found no main effect of

diagnosis (i.e. BD-II). As a result, it would have been unlikely to find (subtle) effects of depression and hypomanic symptomatology, episodes, and cognitive performance within the relatively small patient group.

Only one BD-II patient was experiencing a hypomanic episode. Functional neuroimaging studies have shown differences in regional activation between mania and depression. For instance, during cognitive tasks, depressive episodes are associated with decreased activity in the VPFC (Cousins & Grunze, 2012) and increased ACC activation (Hulvershorn et al., 2012), in contrast with the decreased activation in the VLPFC (e.g. C. H. Chen et al., 2006) and ACC (Hulvershorn et al., 2012) in hypomanic episodes.

In a similar vein to control or test various BD-II states, future studies should use narrowly defined groups (e.g. BD-II hypomania against BD-I mania) as this would elucidate specific features unique to the BD spectrum, as opposed to a general difference against healthy participants (Strakowski et al., 2012). Furthermore, one could combine this with patients with other related diagnoses, such as UD and SZ in order to disentangle the unique differences related to BD.

There could be other variables that better encapsulate BD-II. It could be that pediatric BD-II is substantially different from people over 40 with BD-II, which would tie in with the psychopathology of BD-II. Another idea would be to asses emotional coping/regulation style and/or cognitive style, using the Cognitive Emotion Regulation Questionnaire (CERQ) (Garnefski, Kraaij, & Spinhoven, 2001). Rumination, catastrophizing, and self-blame are strategies often used by people with BD (Green et al., 2011), and could be controlled for. This way, one could characterize the BD-II patients that have the worst symptoms. MacCabe et al. (2010) found that male teenagers that excelled in school had a fourfold increased risk of later BD compared to those with average grades. However, in the same study, teenagers with the poorest grades were also at moderately increased risk of BD (MacCabe et al., 2010). As a result, future studies might benefit from obtaining academic grades / IQ scores from patients with BD. It would be interesting to see if specific genes can be related to the development of BD-II, and to what degree RSFC can act as an endophenotype for said genetic risk.

One could approach and delineate brain networks in BD-II using other analytical methods, such as graph theory (Supekar, Menon, Rubin, Musen, & Greicius, 2008), which has been applied in studies of schizophrenia (e.g. Karbasforoushan, Woodward, 2012) and Alzheimer's disease (Tijms et al., in press). In contrast with the networking method used in the current study, graph metrics includes a clustering coefficient, consisting of densely connected local clusters. This involves a path length to each of the nodes within a cluster.

This allows for a small-world approach e.g. (Watts & Strogatz, 1998). The smaller the path lengths, the more enhanced the sign-propagation speed and synchronizability is between nodes (Watts & Strogatz, 1998). Several studies (Achard, Salvador, Whitcher, Suckling, & Bullmore, 2006; Micheloyannis et al., 2006; Stam, 2004) implicate that graph theory is a suitable way to quantify the topological organization of the human brain (Supekar, Musen, & Menon, 2009). Future studies should combine task-fMRI with rs-fMRI, to assess whether there is a difference in the overall organization of brain networks (clustering hierarchy). It is plausible that differences between BD-II patients and healthy controls are context dependent, and thus network properties might be different from rs-fMRI in task-fMRI. In addition, one could use one of the aforementioned network modeling approaches using structural MRI, where the nodes could represent cortical thickness, which has been done in schizophrenia research (e.g. Pinotsis, Hansen, Friston, & Jirsa, 2013; Zhang et al., 2012). One could then choose tasks known to target emotional and cognitive dyscontrol in BD, such as the emotional-face task. Overall, the findings of the current study indicate that the current methods cannot be used as a diagnostic tool to aid in the early identification of people at risk of BD-II disorder

Conclusion

Contrasting our hypothesis, we report no significant differences in resting-state functional connectivity measures within and between the DMN, TPN, frontal networks and the amygdala (medial temporal lobes) between patients with BDII and healthy controls. Although larger studies with increased power are strongly needed, these findings goes against previous resting-state studies that have found aberrance in the DMN, although most previous studies have been focusing on BD-I. The present results indicate normal functional interactions during rest between brain networks assumed to be involved in emotional regulation, as well as cognition in patients with BDII, which was partly supported by the subtle differences in neuropsychological test performance between groups. Future studies may include a sample of BD-II patients with depressive and especially hypomanic episodes, which can help elucidate both the underpinnings of the diagnosis itself, but also depression and hypomania. Our trend findings indicate that amygdala-DMN connectivity should be investigated further, as well as the superior parietal lobe in relation to other networks, which could be enhanced through other means of network modeling, such as graph theory.

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Appendix

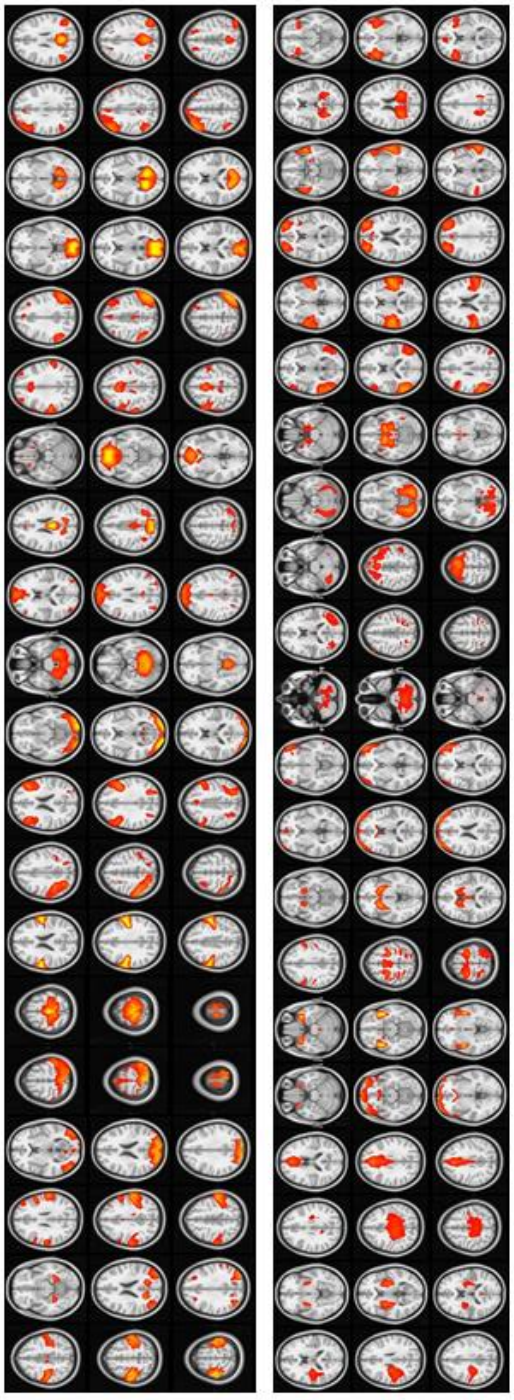

Figure 8. Good components

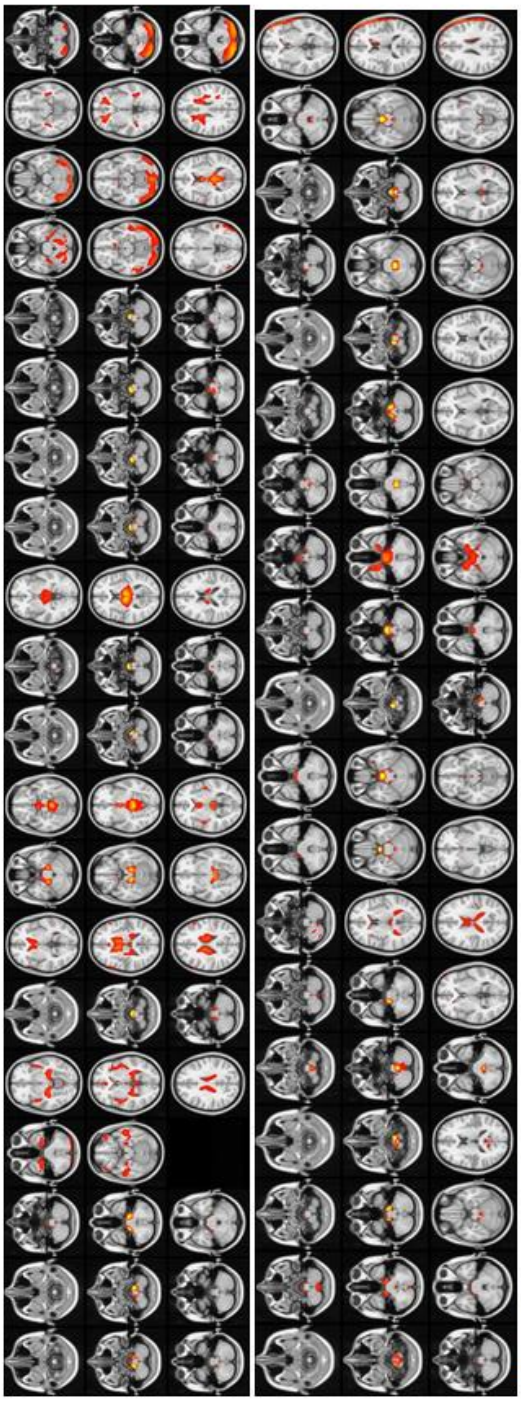

Figure 9. Bad components

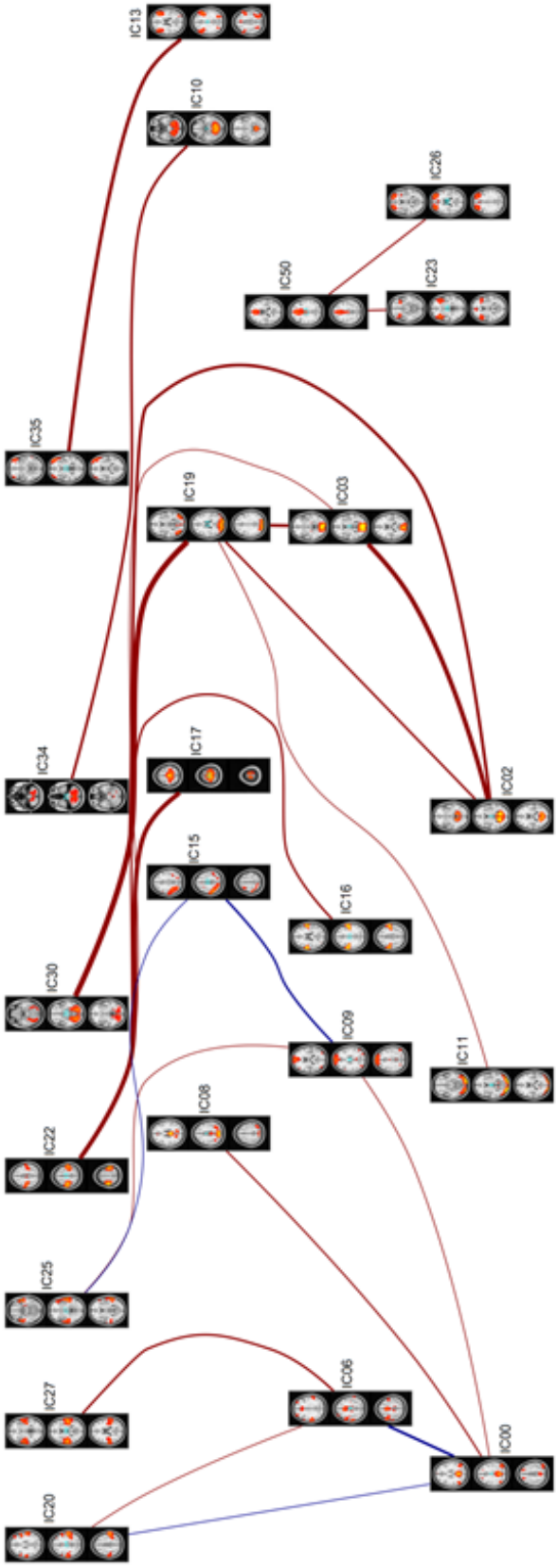

Figure 10. An alternative network plot that shows the correlation between brain networks ($t > |4.0|$) across groups. The colour of the lines represent the direction of the correlation, with blue being negative and red being positive. The thickness of the lines represents the strength of the correlation.