



A framework for interpreting functional networks in schizophrenia

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Some promising genetic correlates of schizophrenia have emerged in recent years but none explain more than a small fraction of cases. The challenge of our time is to characterize the neuronal networks underlying schizophrenia and other neuropsychiatric illnesses. Early models of schizophrenia have been limited by the ability to readily evaluate large-scale networks in living patients. With the development of resting state and advanced structural magnetic resonance imaging, it has become possible to do this. While we are at an early stage, a number of models of intrinsic brain networks have been developed to account for schizophrenia and other neuropsychiatric disorders. This paper reviews the recent voxel-based morphometry (VBM), diffusion tensor imaging (DTI), and resting functional magnetic resonance imaging literature in light of the proposed networks underlying these disorders. It is suggested that there is support for recently proposed models that suggest a pivotal role for the salience network. However, the interactions of this network with the default mode network and executive control networks are not sufficient to explain schizophrenic symptoms or distinguish them from other neuropsychiatric disorders. Alternatively, it is proposed that schizophrenia arises from a uniquely human brain network associated with directed effort including the dorsal anterior and posterior cingulate cortex (PCC), auditory cortex, and hippocampus while mood disorders arise from a different brain network associated with emotional encoding including the ventral anterior cingulate cortex (ACC), orbital frontal cortex, and amygdala. Both interact with the dorsolateral prefrontal cortex and a representation network including the frontal and temporal poles and the fronto-insular cortex, allowing the representation of the thoughts, feelings, and actions of self and others across time.

Keywords: schizophrenia, major depressive disorder, bipolar disorder, functional MRI, voxel-based morphometry, diffusion tensor imaging, default mode network, salience network

INTRODUCTION

Over 120 years ago, Emil Kraepelin made the distinction between dementia praecox, later to be called schizophrenia, and manic-depressive psychosis, later to be referred to as bipolar disorder. Although the distinction has held up well, some limitations have become evident. Kraepelin's suggestion that patients with dementia praecox tend to cognitively deteriorate while manic-depressive patients recover was probably not accurate as we now know that bipolar patients can experience cognitive difficulties. We also now know that there is an excess of relatives with bipolar disorder in schizophrenic proband families as well as an excess of schizophrenic relatives in bipolar proband families and some susceptibility loci are common to both nosological categories (Goodwin and Jamison, 2007; Lichtenstein et al., 2009). Yet the distinction between schizophrenia and bipolar disorder remains in all diagnostic systems and even advocates of a dimensional approach admit that there are non-shared genetic risk factors for schizophrenia and bipolar disorder (Craddock and Owen, 2010).

Although some promising genetic anomalies have been associated with schizophrenia, none account for more than a small

fraction of cases. The challenge of our time is to discover the brain networks underlying schizophrenia and other neuropsychiatric disorders. Almost every region of the brain has been examined in schizophrenic patients with the prefrontal cortex, the anterior cingulate cortex (ACC), temporal structures, the ventral striatum, the thalamus, and the cerebellum most commonly implicated. More than eight models of aberrant cortical-cortical and cortical-subcortical connections between these regions based on pathological, pharmacological, and brain imaging evidence have been proposed. Each provides some explanatory power but none succeed in demonstrating a unique neuronal circuit anomaly in schizophrenia which contrasts with mood disorders (Williamson, 2006).

The early models of schizophrenia were limited by the inability to easily evaluate large-scale brain networks in living patients. Non-human animal models can demonstrate some aspects of psychosis such as dopaminergic hyperresponsivity but fall far short of the phenomenology of schizophrenia because non-humans do not have recursive language or the ability to represent the thoughts, feelings, and actions of self and others

across time. Schizophrenia and bipolar disorders are human disorders (Williamson and Allman, 2011). That changed when it became possible to examine large-scale brain networks with low-frequency spontaneous fluctuations of the blood oxygen level-dependent signal (fMRI). Two anticorrelated networks emerged with this approach—a task-related network associated with attention-demanding tasks and the default mode network associated with stimulus-independent thought in the resting state. The task-related network included mostly frontal and parietal regions while the default mode network included the posterior medial cortices and the ventral and dorsal medial prefrontal cortices (Fox et al., 2005; Fransson, 2005). Subsequently, it became clear that there were multiple resting intrinsic brain networks which could be demonstrated with independent component analysis (ICA) (De Luca et al., 2006; Calhoun et al., 2008).

Williamson (2007) proposed that anomalies in coordination of the default mode and task-related circuits could underlie the pathophysiology of schizophrenia. Subsequently it was proposed that anomalies in the coordination of these networks in schizophrenia were related to a third intrinsic network, the salience network, involving the dorsal anterior cingulate and the fronto-insular cortex (Menon, 2011; Palaniyappan and Liddle, 2012). Menon (2011) took this a step further and suggested that the psychopathology of most major conditions such as schizophrenia, major depression, autism, and anxiety disorders could be accounted for by aberrant intrinsic organization and interconnectivity of the salience network, the default mode network and the central executive network, which is similar to the task-related network. In schizophrenia, structural and functional networks were proposed to affect all three networks. Major depression was suggested to be associated with excessive coupling between the salience and default mode networks leading to an inability to cycle out of internal mental processes to attend to salient tasks.

Others have proposed somewhat different pathways underlying psychopathology. Buckner et al. (2008) proposed two brain systems, the default network and a medial temporal lobe system. The default mode was related to internally focussed tasks such as autobiographical memory, envisioning the future, and conceiving the perspectives of others while the temporal system provided information about prior experience for mental simulations in the medial regions. Integration of information occurs with the convergence of the two networks through the posterior cingulate cortex (PCC). Autism was attributed to anomalies in the development of the default network and schizophrenia was attributed to over-activity in the default mode network. Northoff and Qin (2011) suggested that auditory verbal hallucinations in schizophrenia arise from elevated resting state activity in the auditory cortex which might be related to abnormal modulation of the auditory cortex by anterior cortical midline structures associated with the default mode network. Abnormal resting state activity was also suggested to impact stimulus-induced neural activity in medially situated core systems for self-representation in major depression leading to a “highjacking” of higher cortical affective and cortical functions by lower sub-cortical primary-process emotional systems (Northoff et al., 2011).

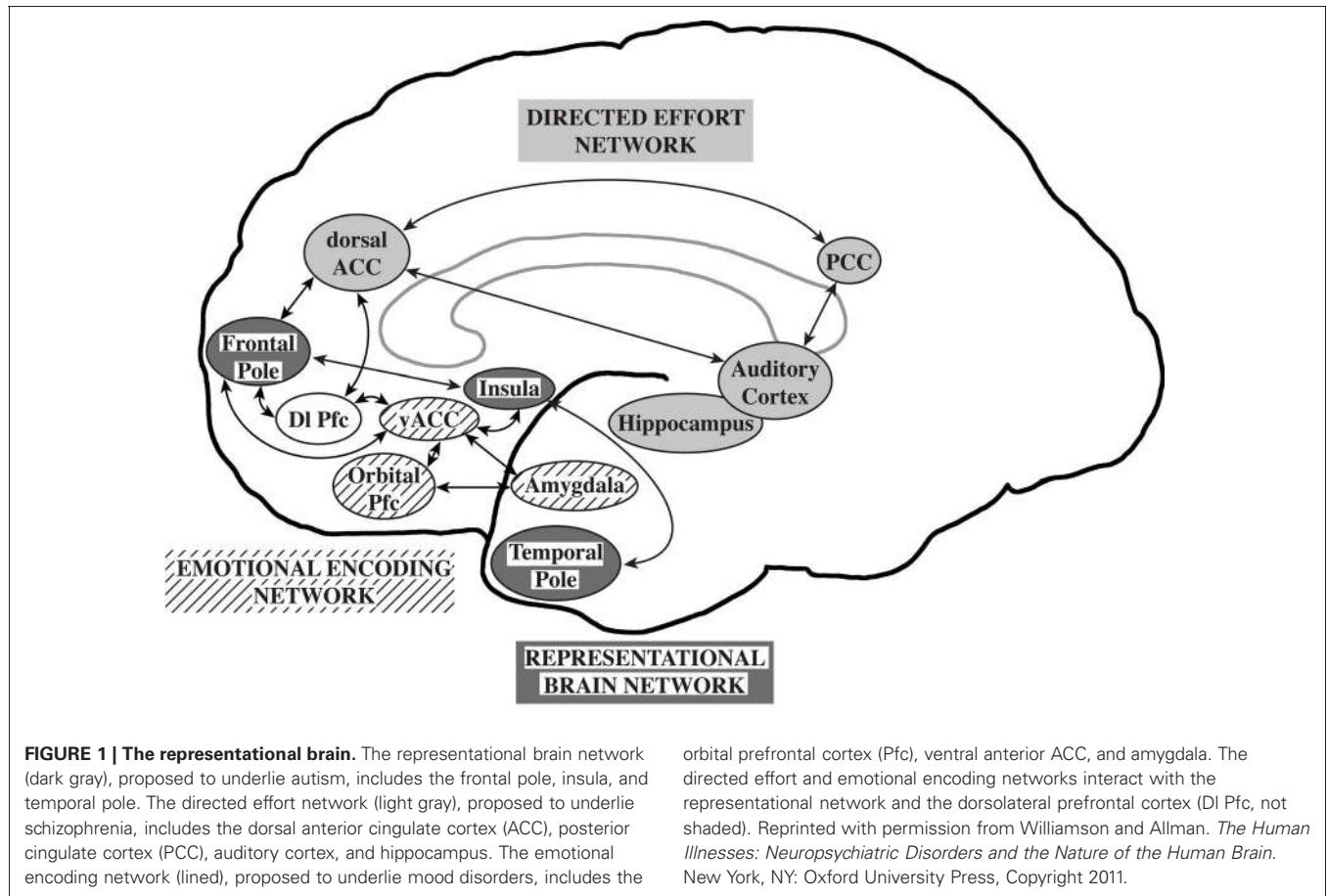
Williamson and Allman (2011) proposed that neuronal circuits underlying neuropsychiatric disorders mirror unique human capabilities. Brain structures such as the frontal pole, temporal pole, and fronto-insular cortex are highly developed in humans and are likely associated with the representation of the thoughts, feelings, and actions of self and others across time (Damasio et al., 2004; Gilbert et al., 2006; Frith, 2007; Craig, 2009). In the human brain, representational networks interact with other networks involved in *directed effort* and *emotional encoding* which have also undergone unique adaptations in the human brain. All three networks interact with the dorsolateral prefrontal cortex allowing the temporal flow of information and behavior. A failure of the representational networks could lead to autism. Schizophrenia was proposed to be related to a failure of the directed effort network which included the dorsal and posterior anterior cingulate cortices, the auditory cortex, and the hippocampus to synchronize with the representational network. Major depression and bipolar disorders were suggested to be associated with a failure of the emotional encoding network, including orbital prefrontal cortex, ventral ACC, and amygdala, to synchronize with the representational network (Williamson and Allman, 2011; **Figure 1**).

Thus, a number of large-scale brain networks have been proposed to underlie schizophrenia and major psychiatric conditions. All models include the default mode network. The salience network models (Menon, 2011; Palaniyappan and Liddle, 2012) emphasize anomalies in this network in coordinating activity between the task-related and default mode networks in schizophrenia and other neuropsychiatric conditions. Buckner et al. (2008) propose a different emphasis on the temporal systems, the default mode network and their integration through the PCC. The central role of the dorsal anterior cingulate, posterior cingulate, and temporal structures in schizophrenia can also be seen in the Northoff and Qin (2011) and Williamson and Allman (2011) models. These models can be tested. If there are anomalies in these networks in schizophrenia, they should be demonstrable with voxel-based morphometry (VBM), diffusion tensor imaging (DTI), and fMRI, which open a window on the morphological and functional characteristics of large-scale networks. The purpose of this paper is to examine the more recent literature utilizing these techniques in schizophrenia and mood disorders in light of these models.

VBM

FINDINGS IN SCHIZOPHRENIA

There are now several meta-analyses of findings in well over 1000 schizophrenic patients. There is an emerging consensus that schizophrenic patients have gray matter reductions in the left medial and superior temporal gyrus, left middle frontal gyrus, ACC, bilateral insular cortex, and thalamus although losses have also been reported in inferior prefrontal and posterior regions (Honea et al., 2005; Ellison-Wright et al., 2008; Glahn et al., 2008; Fornito et al., 2009b; Segall et al., 2009; Ellison-Wright and Bullmore, 2010). Particularly noteworthy are the volume reductions in the ACC which may precede the onset of psychosis in high-risk individuals and are accompanied by reductions in neuronal, synaptic, and dendritic density in post-mortem studies



(Baiano et al., 2007). Some brain abnormalities can be seen in first episode patients (Vita et al., 2006; Fornito et al., 2009a) but there is now overwhelming evidence of that gray matter losses in regions associated with task performance such as the prefrontal, parietal, and temporal cortices become more prominent after several years of illness (DeLisi, 2008; Olabi et al., 2011). Significantly greater frontal, temporal, and parietal gray matter losses in childhood-onset schizophrenic patients have been reported compared to patients with transient psychosis and behavior problems who had similar neuroleptic exposure on follow-up (Gogtay et al., 2004) but it is possible that neuroleptic medications may account for some of the differences (Torrey, 2002; Navani and Dazzan, 2008; Smieskova et al., 2009; Ho et al., 2011).

The widespread nature of gray matter losses in schizophrenia has always been difficult to explain. However, both the salience models (Menon, 2011; Palaniyappan and Liddle, 2012) and the extended models (Buckner et al., 2008; Northoff and Qin, 2011; Williamson and Allman, 2011) involving the dorsal anterior and posterior cingulate, and temporal structures would predict this. If salience network fails to appropriately engage the executive control and default mode networks, decreased gray matter activity and potentially loss would be expected. Similarly a failure of the directed effort network would be expected to be associated with widespread gray matter loss by virtue of connections with basal ganglia-thalamocortical networks which effect action via

glutamatergic cortical-subcortical pathways (Williamson, 2006). However, the volume reductions in the anterior cingulate, which may precede the onset of psychosis in high risk individuals, points more to the anterior cingulate as the primary cause of the later more widespread changes. The anterior cingulate is closely connected to the posterior cingulate, temporal structures and the insula, implicating all models. The finding that may be difficult for the Williamson and Allman (2011) model to account for is the inferior frontal gray matter loss. However, this might be explained by the reciprocal relationship between the dorsal ACC and inferior prefrontal regions (Mayberg et al., 1999). Reciprocal changes in parallel networks including the representational and emotional encoding networks would be expected.

FINDINGS IN MOOD DISORDERED PATIENTS

There has been considerable heterogeneity in VBM in patients with major depressive and bipolar disorders (Campbell et al., 2004; Haldane and Frangou, 2004; McDonald et al., 2004; Videbech and Ravnkilde, 2004; Strakowski et al., 2005; Hajek et al., 2008; Savitz and Drevets, 2009; Bora et al., 2010; Ellison-Wright and Bullmore, 2010). However, there is a recurrent theme of elevated activity and volume loss in the hippocampus, orbital, and ventral prefrontal cortex in patients with major depressive disorder and bipolar disorder (Savitz and Drevets, 2009). The amygdala in contrast is often found to be increased in volume in

older bipolar patients and either decreased or unchanged in major depressive disorder. Volume losses, particularly in ventral prefrontal regions, are more evident in patients with a positive family history of mood disorders (Hajek et al., 2008). Although there is some overlap with regions showing deficits in schizophrenia, the pregenual cingulate cortex (anterior Brodmann area 24) was found to be reduced in studies of bipolar but not schizophrenic patients (Bora et al., 2010). Interestingly, treatment with mood stabilizing agents has been associated with enlargement of gray matter volumes (Nakamura et al., 2007). Treatment with lithium has been associated with a more selective increase in regions which were found to be reduced in bipolar patients (Bora et al., 2010).

These studies suggest that mood disordered patients demonstrate a pattern of VBM changes predominately in the orbital and ventral prefrontal regions and amygdala. Structural changes in these regions differ from the pattern in schizophrenia and are consistent with the Williamson and Allman (2011) and Northoff et al. (2011) models. The Menon (2011) model has more difficulty accounting for these changes. If there is excessive coupling of the salience network and default mode network in mood disorders, the specific structural changes in the orbital and ventral prefrontal regions which are not part of the salience network or the default mode network would not be expected. Structural changes in the salience network might be expected and they do not seem to be found.

DTI

FINDINGS IN SCHIZOPHRENIC PATIENTS

DTI has been applied widely in schizophrenia research (Kanaan et al., 2005; Kubicki et al., 2007; Kyriakopoulos et al., 2008; White et al., 2008; Ellison-Wright and Bullmore, 2009; Bora et al., 2011; Patel et al., 2011). Fractional anisotropy (FA) or the degree to which diffusion is directionally hindered is the most widely used index of white matter integrity in these studies. As in the morphometry studies, considerable heterogeneity has been found. However, most studies have found widespread FA reductions in the cingulate bundle, corpus callosum, and frontal and temporal white matter. In a careful meta-analysis of the co-ordinates of FA differences, significant FA reductions were present in predominantly two regions: the left frontal deep white matter and the left temporal deep white matter (Ellison-Wright and Bullmore, 2009). In the left frontal lobe, the white matter tracts involved interconnected the frontal lobe, thalamus, and cingulate gyrus while in the temporal lobe the white matter tracks involved interconnected the frontal lobe, insula, hippocampus-amygdala, temporal, and occipital lobe. Although FA deficits are present in many first episode, never-treated patients, there is some evidence of progressive deterioration (Mori et al., 2007; Cheung et al., 2008; Zou et al., 2008b; Lee et al., 2009; White et al., 2011). FA anomalies have been associated with chronic illness, negative symptoms, and hallucinations (Seok et al., 2007; Shergill et al., 2007; Skelly et al., 2008; White et al., 2008; Rotarska-Jagiela et al., 2009; Bora et al., 2011).

White matter anomalies in tracts connecting frontal lobe, thalamus, and cingulate gyrus would be consistent with hypothesized dysfunction of the directed effort network in the Williamson and

Allman (2011) model. Directed effort requires action mediated by basal ganglia-thalamocortical networks that include these structures. White matter changes in the temporal lobe interconnecting the frontal lobe, insula, and hippocampus-amygdala would also be consistent with this model and the Buckner et al. (2008) model. Both models emphasize connections between the brain regions associated with mental simulations and the temporal lobes. The salience models might be expected to be associated with anomalies in tracts connecting the cingulate cortex and insula with task-activated and default mode regions but connections to the hippocampus and thalamus are better accounted for by a deficit in the directed effort network. All models would have difficulty accounting for the occipital anomalies.

FINDINGS IN MOOD DISORDERED PATIENTS

Never-treated and medicated patients with major depressive disorder have demonstrated the ACC and medial prefrontal FA deficits but studies have been inconsistent with deficits also noted in the internal capsule, inferior parietal lobe, occipital lobe, and temporal regions (Li et al., 2007; Ma et al., 2007; Zou et al., 2008a; Abe et al., 2010; Cullen et al., 2010; Korgaonkar et al., 2011; Wu et al., 2011; Zhou et al., 2011). However, a hypothesis driven study demonstrated lower FA in the white matter tract connecting the right subgenual ACC with the right amygdala (Cullen et al., 2010). Most but not all studies have reported association between severity of symptoms and FA deficits (Li et al., 2007; Zou et al., 2008a; Korgaonkar et al., 2011; Zhou et al., 2011). A recent meta-analysis of 10 studies of bipolar disorders identified two significant clusters of decreased FA on the right side. The first was located in the parahippocampal gyrus and the second was located close to the subgenual ACC (Vedrine et al., 2011). Some of these anomalies may be state-dependent (Zanetti et al., 2009; Benedetti et al., 2011).

While there is considerable heterogeneity, the most consistent DTI findings in mood disordered patients involve the subgenual ACC and the amygdala, a pattern which contrasts with that found in schizophrenic patients. The Menon (2011) model does not provide a good explanation for this finding. If the salience network and default mode networks are excessively coupled, one would not predict anomalous connections between the subgenual prefrontal cortex and amygdala. However, the Williamson and Allman (2011) model would predict this as these are key nodes of the emotional encoding network. The Northoff et al. (2011) model would predict subgenual anterior cingulate anomalies but not necessarily anomalies in connections with the amygdala. Thus, the majority of DTI anomalies involve regions involved in emotional encoding although studies are limited and there have been few direct comparisons between mood disordered and schizophrenic patients.

fMRI INTRINSIC NETWORKS

FINDINGS IN SCHIZOPHRENIA

Task-related network deficits have long been associated with schizophrenia (Williamson, 2006, 2007). However, there is evidence that the default mode network may be abnormal in schizophrenia as well. Unfortunately, the first three studies published within a few months of each other produced somewhat

inconsistent results. Zhou et al. (2007a) showed reduced functional connectivity between the bilateral dorsolateral prefrontal cortices and the parietal lobe, PCC, thalamus, and striatum in schizophrenic patients. Enhanced functional connectivity was found between the left dorsolateral prefrontal cortex and the left mid-posterior temporal lobe, and paralimbic regions. Garrity et al. (2007) reported spatial differences in the default mode network, particularly in the frontal, anterior cingulate, and parahippocampal gyri. Bluhm et al. (2007) found that schizophrenic patients had significantly less correlation between the spontaneous slow activity in the PCC and that in the lateral parietal, medial prefrontal, and cerebellar regions using a seed-based technique.

There are now numerous studies suggesting anomalies in the default network and other intrinsic networks in schizophrenia which have been reviewed elsewhere (Williamson, 2007; Greicius, 2008; Broyd et al., 2009; Calhoun et al., 2009). The subsequent literature has also been inconsistent but the majority of studies have shown reduced task-related suppression of the default network (Zhou et al., 2007b, 2008; Jafri et al., 2008; Pomarol-Clotet et al., 2008, 2010; Bluhm et al., 2009a; Jann et al., 2009; Kim et al., 2009; Park et al., 2009; Whitfield-Gabrieli et al., 2009; Hoptman et al., 2010; Ke et al., 2010; Lui et al., 2010; Lynall et al., 2010; Mannell et al., 2010; Rotarska-Jagiela et al., 2010; Welsh et al., 2010; White et al., 2010; Hasenkamp et al., 2011; Jang et al., 2011; Repovs et al., 2011; Schneider et al., 2011; Swanson et al., 2011; Wang et al., 2011). Both increased and decreased connectivity has been found in the default network. The amplitude of low-frequency fluctuations (ALFF) have been reported to be decreased in never-treated patients in medial prefrontal regions (Huang et al., 2010). ALFF normalizes with antipsychotic therapy (Lui et al., 2010; Sambataro et al., 2010).

Garrity et al. (2007) reported that activity in the medial prefrontal, temporal, and cingulate gyri correlated with positive symptoms while Bluhm et al. (2009a) found that patients with positive symptoms showed increased connectivity between the retrosplenial cortex and auditory processing regions. Rotarska-Jagiela et al. (2010) reported that aberrant functional connectivity in the default mode network correlated with the severity of hallucinations and decreased hemispheric separation of fronto-parietal activity correlated with disorganization symptoms. Patients who have persistent auditory verbal hallucinations (Wolf et al., 2011) have been reported to have increased connectivity in bilateral temporal regions and decreased connectivity in the cingulate cortex within the speech-related network. In networks associated with attention and executive control, patients demonstrated abnormal connectivity in the precuneus and right lateral prefrontal areas. Auditory verbal hallucination severity correlated with the functional connectivity in the left lateral cingulate, left superior temporal gyrus, and right lateral prefrontal cortex.

Why are the findings so inconsistent in schizophrenic patients? Part of the problem may be different analysis techniques. Seed-based and independent component analyses do not always produce the same result. Another reason may be that the default network is not one network but likely scores of networks; only a few of which might be affected at any point of illness or in any particular individual. Resting network activity is also found

during some tasks and there appears to be a pattern of reduced distal and enhanced local connectivity in cognitive control networks in schizophrenic patients which correlates with cognitive performance (Repovs et al., 2011). Other brain networks are likely involved as well. Intrinsic network anomalies have been reported in basal-ganglia thalamocortical networks and language and auditory networks (Welsh et al., 2010; Liemburg et al., 2012). Saliency network anomalies were reported in one study (White et al., 2010) but no differences were observed in the salience network in another study (Woodward et al., 2011).

Interestingly, schizophrenic patients appear to activate circuits normally involved in retrieving other-related information when processing self-generated information (see Figure 2; Wang et al., 2011). Failure to deactivate default mode regions has been found to correspond to gray matter losses in the dorsal ACC and medial prefrontal regions and DTI anomalies in medial prefrontal and hippocampal connectivity (see Figures 3 and 4; Zhou et al., 2008; Pomarol-Clotet et al., 2010; Skudlarski et al., 2010; Salgado-Pineda et al., 2011). Skudlarski et al. (2010) reported that DTI connectivity was nearly uniformly decreased in schizophrenic patients, functional connectivity was lower in

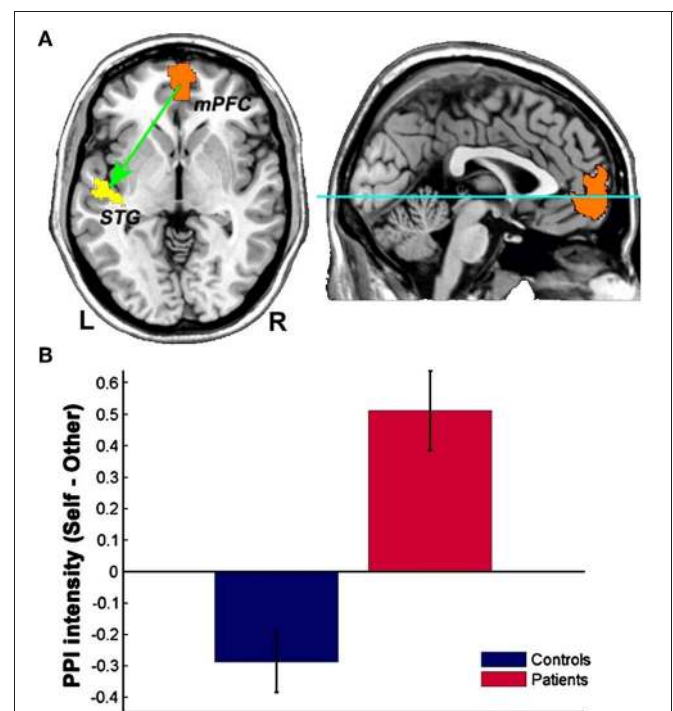
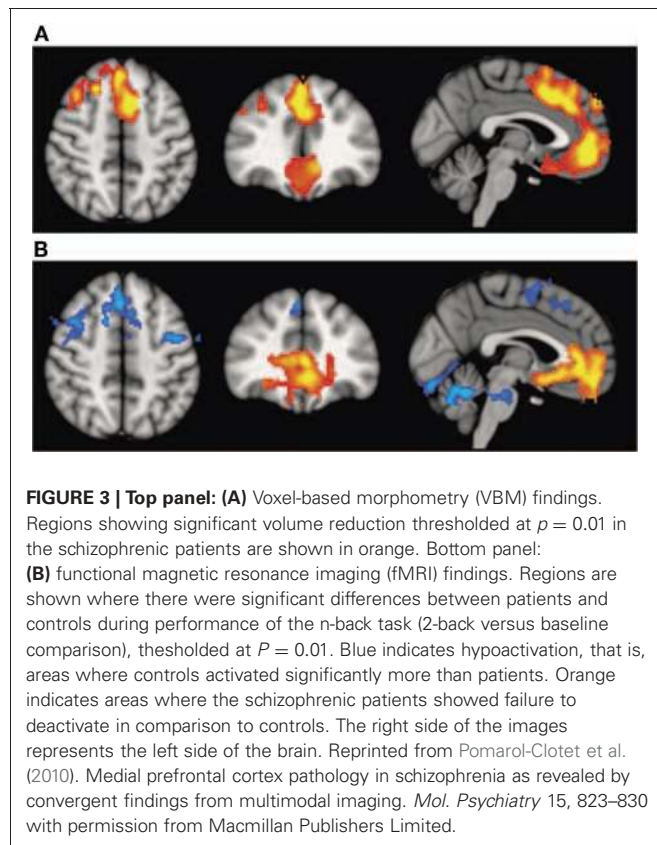


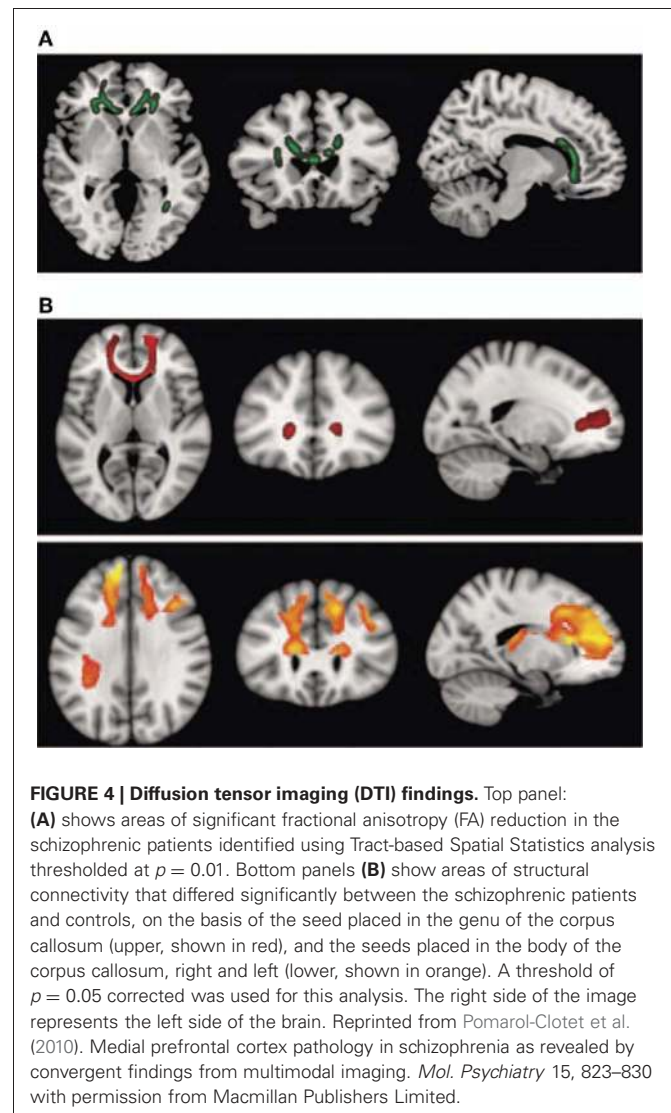
FIGURE 2 | Changes in functional connectivity with the medial prefrontal cortex in schizophrenia. The psychophysiological interaction (PPI) analysis revealed that functional connectivity from the medial prefrontal cortex to the left superior temporal gyrus is significantly modulated by source memory condition (A) By averaging the PPI intensity over the voxels within the significant cluster for each subject, a significant interaction effect was found: higher connectivity is observed in the Self condition in patients with schizophrenia, whereas healthy subjects display higher connectivity in the Other condition (B) Reprinted from Wang et al. (2011). Aberrant connectivity during self-other source monitoring in schizophrenia. *Schizophr. Res.* 125, 136–142 with permission from Elsevier.



the middle temporal gyrus and higher in the cingulate and thalamus. Schizophrenic patients also showed decoupling between structural and functional connectivity that could be localized to networks originating in the PCC as well as the task-related network in this study.

In summary, there appears to be agreement that schizophrenic patients have difficulties deactivating the default mode network. However, both increased and decreased connectivity have been reported within the default network, perhaps reflecting of reduced distal and enhanced local connectivity in cognitive control networks in schizophrenic patients (Repovs et al., 2011). Findings in the dorsal anterior cingulate and medial prefrontal cortex are prominent and may correlate with structural anomalies on VBM and DTI (Zhou et al., 2008; Pomarol-Clotet et al., 2010; Skudlarski et al., 2010; Salgado-Pineda et al., 2011). From these studies it is also apparent that many networks are abnormal in schizophrenia in addition to the default mode network. Anomalies in the language networks and basal ganglia-thalamocortical networks have been reported (Welsh et al., 2010; Liemburg et al., 2012) but findings in the salience network are mixed (White et al., 2010; Woodward et al., 2011).

How do intrinsic network findings relate to the proposed models of schizophrenia? On the whole, they are consistent with the extended models of large-scale network anomalies in schizophrenia. The dorsal anterior and posterior cingulate and auditory cortex are key nodes of the directed effort network (Williamson and Allman, 2011). However, there is support for the Buckner et al.



(2008) and Northoff and Qin (2011) models in that temporal and PCC and language processing regions are associated with connectivity abnormalities. In our view the salience models do not fare quite so well. There is no clear-cut abnormality in the salience network to date although this may remain to be determined. A further difficulty is the obvious involvement of other networks such as the language network which does not fit easily into the three networks proposed by Menon (2011).

FINDINGS IN MOOD DISORDERED PATIENTS

Resting state abnormalities have been reported in both major depressive and bipolar disorder patients (Greicius, 2008; Broyd et al., 2009; Hasler and Northoff, 2011). Major depressive disorder patients have been found to have both increased and decreased connectivity in the default mode network but differences from comparison subjects most often included subgenual and reward processing regions (Greicius et al., 2007; Bluhm et al., 2009b; Cullen et al., 2009; Grimm et al., 2009, 2011; Sheline et al., 2009, 2010; Veer et al., 2010; Berman et al., 2011; Hamilton et al., 2011;

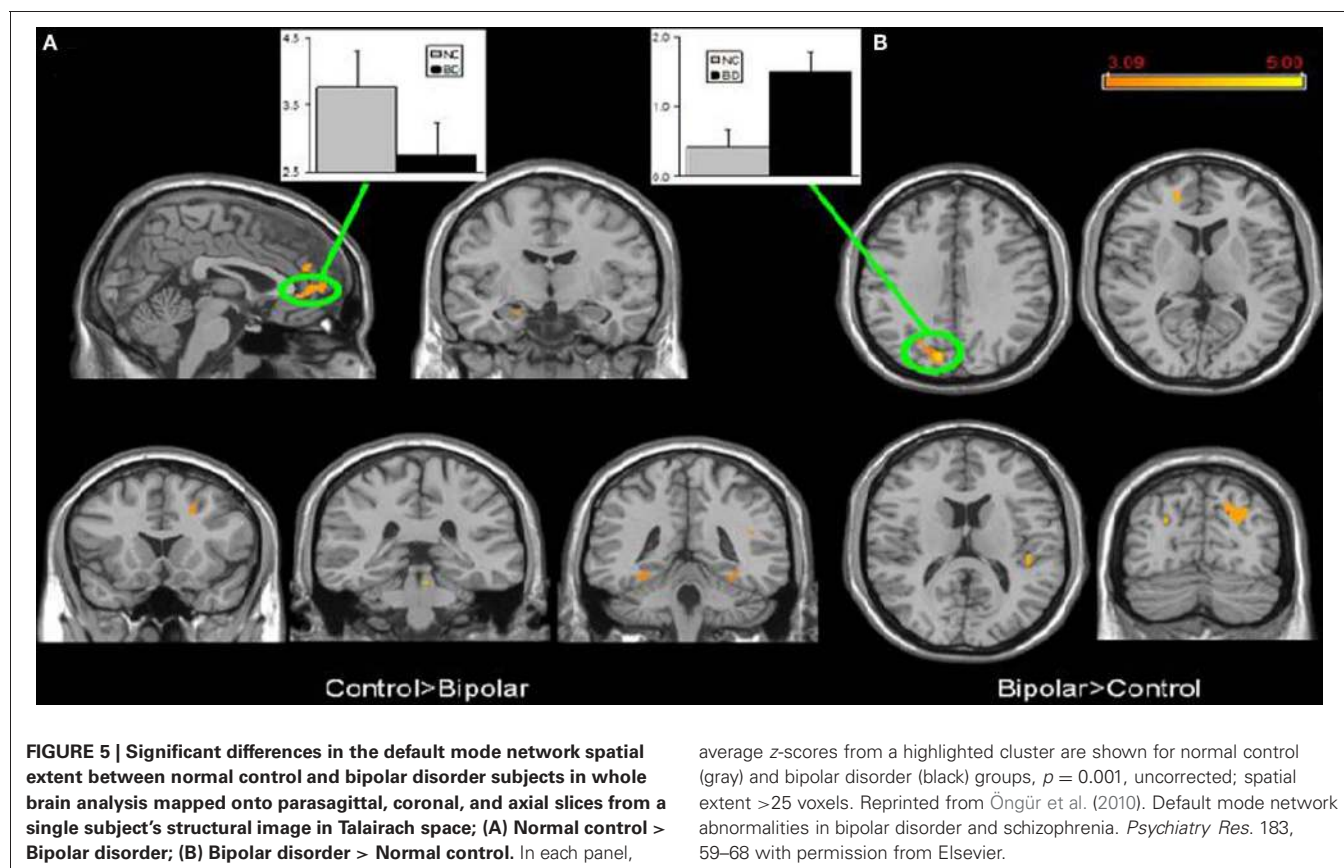
Peng et al., 2011; Zhang et al., 2011). Bipolar disorder patients also demonstrated anomalies in resting networks mostly involving ventral prefrontal connections to the amygdala (Calhoun et al., 2008; Anand et al., 2009; Chepenik et al., 2010; Dickstein et al., 2010; Öngür et al., 2010; Sui et al., 2011). Selective serotonin reuptake inhibitor administration has been indicated to reduce resting state functional connectivity in the dorso-medial prefrontal cortex (McCabe et al., 2011). Consequently some differences may be associated with medication effects but, on the whole, mood disordered patients present a different pattern of intrinsic network anomalies affecting predominately but not exclusively emotional encoding regions.

Few studies have examined both bipolar and schizophrenic patients. However, subgenual and medial prefrontal anomalies were reported in bipolar patients and dorsal medial prefrontal anomalies in schizophrenic patients in a recent study of both disorders (see **Figures 5** and **6**; Öngür et al., 2010). In a subsequent seed-based analysis of largely the same data, distinctive patterns emerged. The bipolar group had positive correlations between the medial prefrontal cortex and insular and ventral prefrontal regions. Both schizophrenic and bipolar patients failed to exhibit significant anticorrelation between the medial prefrontal cortex and dorsolateral prefrontal cortex seen in controls, perhaps accounting for cognitive deficits seen in both disorders (Chai et al., 2011).

Although preliminary, there have been some attempts to utilize intrinsic network differences to classify patients on the basis

of ICA analysis. It is difficult to translate these components into particular functional networks because of the complex nature of comparisons but differences have been found to have a sensitivity and specificity of 90 and 95%, respectively, classifying schizophrenia and bipolar disorder on the basis of resting networks (Calhoun et al., 2008). A more recent study (Calhoun et al., 2012) reported that bipolar patients showed more prominent changes in the ventromedial and prefrontal default mode regions while schizophrenic subjects showed differences mostly in posterior default mode regions. The ventral ACC was one of the few regions that distinguished schizophrenic from bipolar disorder patients. The medial prefrontal cortex and ACC were less connected to inferior frontal and insular regions in both schizophrenic patients and bipolar patients. “Fusing” resting data with DTI was also associated with promising levels of discrimination between schizophrenic and bipolar disorder (Sui et al., 2011).

These studies suggest that the pattern of intrinsic functional connectivity is different in bipolar disorder than in schizophrenia. Bipolar disorder patients are more likely to show ventral prefrontal anomalies while schizophrenic patients are more likely to have dorsal anterior cingulate and prefrontal cortex anomalies. This is in keeping with the Williamson and Allman (2011) model, although it is also consistent with Northoff et al. (2011). The finding of predominantly posterior default mode differences in schizophrenic patients would be consistent with both the Williamson and Allman (2011) and Buckner et al. (2008) models.



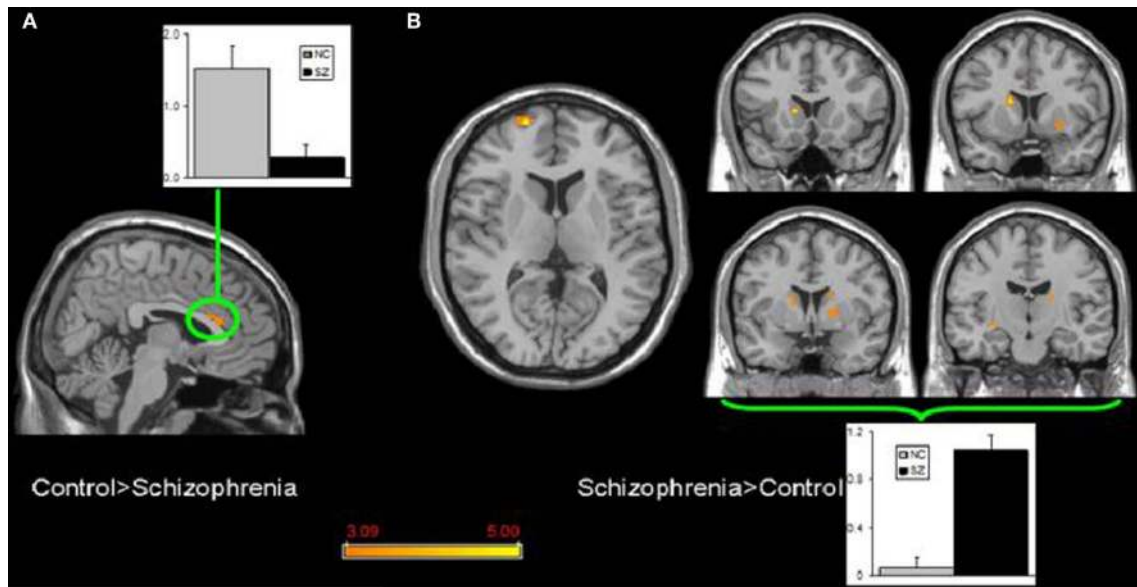


FIGURE 6 | Significant differences in the default mode network spatial extent between normal control and schizophrenia subjects in whole brain analysis mapped onto parasagittal, coronal, and axial slices from a single subject's structural image in Talairach space; (A) Normal control > Schizophrenia where the only finding is in the anterior cingulate cortex; (B) Schizophrenia > Normal control where multiple clusters are seen

throughout the basal ganglia. Average z-scores are shown for normal control (gray) and schizophrenia (black) groups from a highlighted cluster in (A), and from a group of clusters in the basal ganglia in (B). $p = 0.001$, uncorrected; spatial extent >25 voxels. Reprinted from Öngür et al. (2010). Default mode network abnormalities in bipolar disorder and schizophrenia. *Psychiatry Res.* 183, 59–68 with permission from Elsevier.

The one thing that does not emerge from these studies is a prominent abnormality in the salience network in either schizophrenic or bipolar patients. There are differences in the insula but the insula is part of a wider network involved in awareness, not just salience, leading Williamson and Allman (2011) to include it as part of the representational brain network.

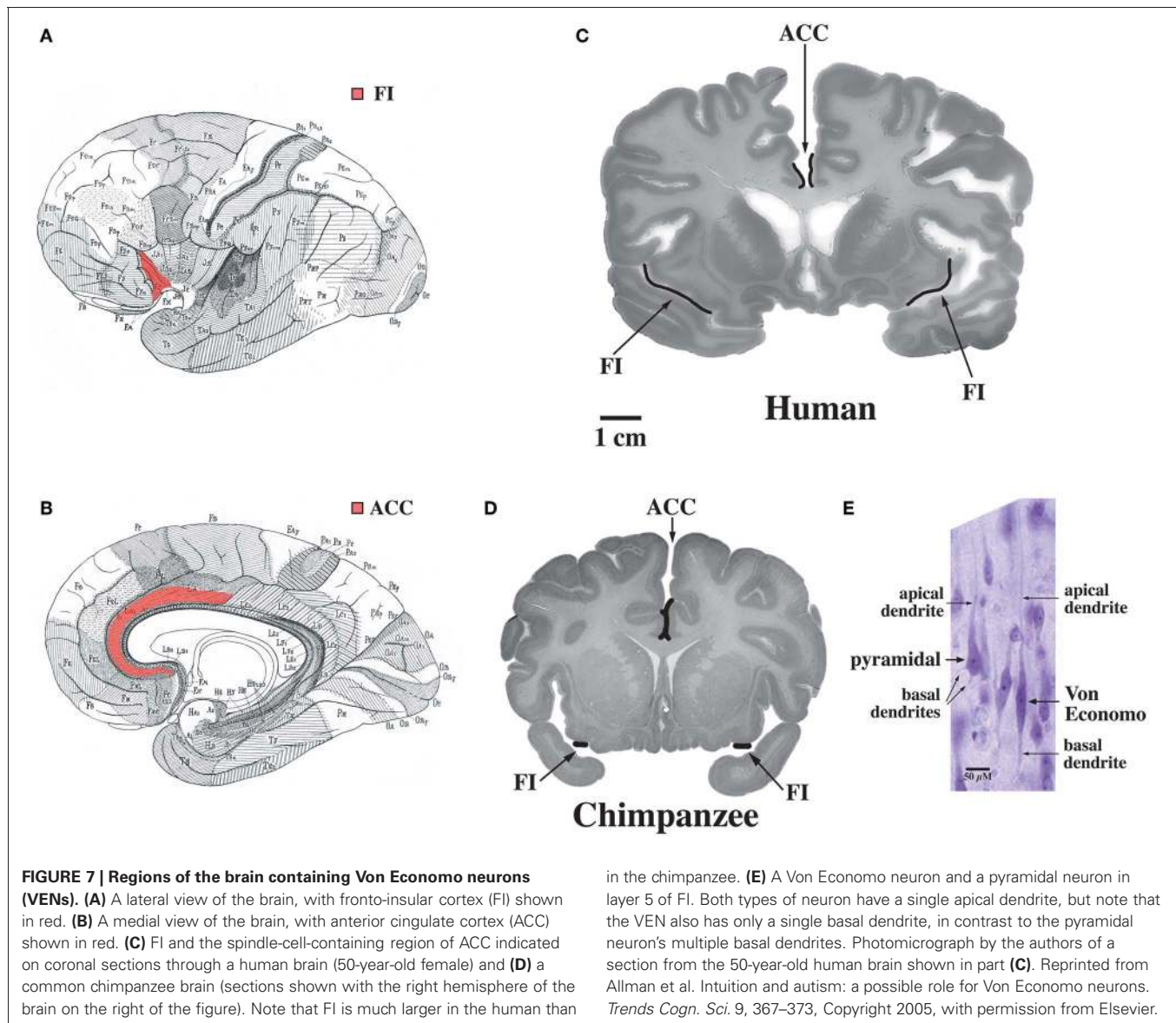
NETWORK ANOMALIES UNDERLYING SCHIZOPHRENIA AND MOOD DISORDERS

Although we have known for some time that schizophrenic patients demonstrate multiple deficits in various task-related networks, the characterization of the default mode network has provided a new way to evaluate abnormalities in internal thinking processes which are associated with this disorder. However, findings related to the default mode network in schizophrenia have been inconsistent. This is probably not surprising because the deficits demonstrated in task-related networks in schizophrenic patients are widespread and often contradictory as well (Williamson, 2006). The default mode network is very large and probably made up of as many complex networks as the task-related network.

The characterization of the salience network is an important step forward (Seeley et al., 2007). This network possibly provides a piece of the puzzle which was missing, that is, what modulates and controls the switch from the default network to the task-related network. It is reasonable to propose that this network along with the default mode network and task-related networks must be affected in many psychiatric disorders including schizophrenia (Menon, 2011; Palaniyappan and Liddle, 2012).

There is a rich pathophysiological literature implicating salience in schizophrenia (Kapur, 2003; Palaniyappan and Liddle, 2012). However, the question is whether these networks are sufficient to account for schizophrenia and other neuropsychiatric disorders? The structural and functional data reviewed above would suggest that they are not. The salience network does not emerge as being uniquely affected in schizophrenia nor do changes in these three networks separate schizophrenia from mood disorders.

The default mode network is highly adapted in the human brain and undergoes extensive development throughout the early years of life in concert with uniquely human capabilities such as theory of mind and language (Fair et al., 2007, 2008; Fransson et al., 2007; Rilling et al., 2007; Williamson and Allman, 2011). These specializations are possibly related to the abundance in humans of Von Economo neurons which are distributed throughout the dorsal and ventral ACC (ACC, see Figure 7, Allman et al., 2005). Dorsal-caudal locations of the anterior cingulate map onto frontoparietal attention networks while rostral-ventral locations map onto negatively correlated networks including the default mode network (Margulies et al., 2007). While the projections of Von Economo neurons are not yet known, it is highly likely that they project to the medial prefrontal cortex (frontal pole), a region known to be associated with information processing when more than one course of action may be required, such as representing the thoughts, actions, and feelings of others across time (Ramnani and Owen, 2004; Gilbert et al., 2006). Medial prefrontal regions and the right fronto-insula are less activated during social tasks in autism spectrum disorder patients (Di Martino et al., 2009). The ACC is also closely connected to the fronto-insula



which may be involved with social behaviors. In Williams syndrome patients, hypersocial behavior correlated with structural and functional imaging anomalies in the right anterior insula (Jabbi et al., 2012). Thus, the dorsal and ventral ACC are closely connected to regions involved in representing self and others. Could unique adaptations of the dorsal and ventral anterior cingulate possibly mediated by Von Economo neurons make the human brain vulnerable to schizophrenia and bipolar disorders?

The dorsal ACC has been implicated with the dorsolateral prefrontal cortex in the control of directed effort (Paus et al., 1998; Allman et al., 2001; Passingham et al., 2010). There is an extensive literature implicating functional, structural, and post-mortem anomalies in schizophrenic patients in these regions (Benes, 2000; Tamminga et al., 2000; Williamson, 2006; Williamson and Allman, 2011). Patients who damage this part of the brain are flat and amotivated (Damasio and Van Hoesen, 1983). The dorsal ACC and dorsolateral prefrontal cortex may also regulate

cortical dopaminergic activity via projections to the brain stem (Lewis and González-Burgos, 2006). Never-treated, first episode schizophrenic patients have increased levels of glutamatergic metabolites in this region and the thalamus which decrease over time in association with gray matter loss and decline in social functioning (Bartha et al., 1997; Théberge et al., 2002; Aoyama et al., 2011). It is of note that schizophrenic patients given N-methyl-D-aspartate antagonists show an increase in metabolism and glutamatergic metabolites in this region as well as an increase in symptoms (Lahti et al., 1995; Rowland et al., 2005).

The dorsal ACC is closely connected to speech processing regions anatomically and functionally in humans (Barbas et al., 1999; Hunter et al., 2006; Yuki and Shibata, 2009). It is also connected to the PCC and hippocampus. All of these regions have been associated with anomalies in schizophrenia. It is of note that these regions closely interact with basal ganglia-thalamocortical networks to effect action via glutamatergic cortical-subcortical

pathways, which are regulated by dopamine, and are implicated in schizophrenia as well (Williamson, 2006). If the directed effort network fails to be fully engaged with the representational network then thoughts, feelings or actions may be perceived to belong to someone else. Thoughts may also be perceived as hallucinations and fear associated with these symptoms may lead to paranoia, all key symptoms of schizophrenia. The network depends on the coordinated activity of the dorsal ACC, PCC, auditory cortex and hippocampus so dysfunction at any of these nodes could disrupt the functioning of the network. Although there is preliminary evidence of decreased Von Economo neuron density in the anterior cingulate in early onset schizophrenia (Brüne et al., 2010), dysfunction would not necessarily be related to a loss of Von Economo neurons.

The ventral ACC is part of a network involved in emotional regulation including the orbitofrontal cortex, medial prefrontal cortex, and amygdala. Major depressive and bipolar disorders are clearly associated with anomalies in these regions. Histopathological, structural, and activation abnormalities during the presentation of emotional stimuli and reward paradigms have been reported in the posterior lateral and medial orbitofrontal cortex (Phillips et al., 2003; Drevets, 2007). Depression severity is inversely correlated with activity in these regions. Activity in the posterior ventral medial orbitofrontal cortex is increased in depression and decreased by antidepressant medications. Some parts of the orbitofrontal cortex inhibit while other regions facilitate emotional expression suggesting that the orbitofrontal cortex may be the ventral input to the representational brain (Drevets, 2007; Myers-Schulz and Koenigs, 2012). If emotional evaluative regions in the orbitofrontal cortex fail to engage with the representational network, enhanced output from posterior ventral medial structures could lead to changes

in the emotional response system mediated by the amygdala in depression while mania could result from decreased output from the posterior ventral medial prefrontal cortex to the amygdala or increased output to the amygdala from subgenual ventral medial prefrontal, positive emotion-enhancing regions (Myers-Schulz and Koenigs, 2012). Thus, depressed patients experience negative thoughts about themselves, the world, and the future as well as negative affect, distinguishing them from apparent depression in animals.

In the search for intrinsic brain networks which underlie schizophrenia and mood disorders, we suggest that it makes sense to think of distinct dorsal and ventral networks that interact with the representational networks and the dorsolateral prefrontal cortex (Williamson and Allman, 2011). In our view the suggestions of Buckner et al. (2008) and Northhoff and Qin (2011) are consistent with this model. Both hypothesize aberrant coordination between the regions involved in mental simulation and auditory processing which may be mediated by the posterior cingulate. It should also be recognized that earlier models (Williamson, 2006), which integrate some of these regions, cannot be excluded at this point. Large-scale intrinsic network models are a work in progress but there is reason to believe that larger studies utilizing both structural and functional measurements may one day illuminate a neural basis for Kraepelin's astute clinical observations.

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