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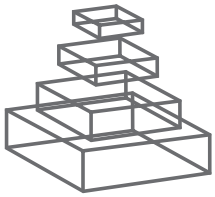

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COGNITION AND NEUROIMAGING IN SCHIZOPHRENIA

Hosted By:
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Last year we edited a Frontiers Research Topic on "An update on neurocognitive impairment in schizophrenia and depression". We are now following-up this initiative with a new invitation, focusing on "Cognition and neuroimaging in schizophrenia", thus narrowing the focus on schizophrenia, but expanding the focus to functional and structural neuroimaging to reveal the underlying neuronal architecture behind cognitive impairments. A second focus is closing in on auditory hallucinations and "hearing voices" in the general population by non-psychotic individuals. This has become an important topic in research on schizophrenia and could cast new light on commonalities in symptom-like behavior in non-clinical and clinical "voice hearers" and hallucinating individuals, that in turn could say something about a continuum of symptoms. A third focus is on network connectivity and connectome mapping in schizophrenia using novel state-of-the-art neuroimaging analysis tools. Schizophrenia has long been considered a disease of disconnectivity and thus special emphasis is given to work which addresses the schizophrenia macro-connectome including both functional and structural aspects. Central to such an approach are recent discoveries of intrinsic resting state networks that are task independent, and/or activated in the absence of a cognitive task. Possible impairments in the dynamic interactions between large-scale networks may prove new insights into the neurobiology of schizophrenia and schizophrenia symptoms.

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EDITORIAL
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Cognition and neuroimaging in schizophrenia

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In 2010 we edited a Frontiers Special Topic on "An update on neurocognitive impairment in schizophrenia and depression" (Hugdahl and Calhoun, 2010). We follow-up this initiative with a new Special Topic focusing on "Cognition and neuroimaging in schizophrenia," thus narrowing the focus to schizophrenia, but expanding the focus to functional and structural neuroimaging to reveal the underlying neuronal architecture behind cognitive impairments. Schizophrenia has long been considered a disease of disconnectivity and thus special emphasis is given to work which addresses the schizophrenia macro-connectome including both functional and structural aspects. Central to such an approach are recent discoveries of intrinsic resting state networks that are task independent, and/or activated in the absence of a cognitive task. Possible impairments in the dynamic interactions between large-scale networks may provide new insights into the neurobiology of schizophrenia and schizophrenia symptoms. Recent research has also revealed the neuronal organization of auditory hallucinations, and how aberrant cortical network connectivity may contribute to the experience of auditory hallucinations.

We present 10 articles with three general sub-themes. The first four articles focus on ways to characterize schizophrenia and analyze data using a proposed framework, the search for a relationship between imaging and symptomatology, and the use of multimodal imaging and genetics data. The next three articles focus on auditory hallucinations and "hearing voices" in the general population by non-psychotic individuals. This has become an important topic in research on schizophrenia and could cast new light on commonalities in symptom-like behavior as well as hallucinating individuals, that in turn could say something about a continuum of symptoms. The final three articles focus on network connectivity and connectome mapping in schizophrenia. Examples include a study of the up and down regulation of task-related networks, a study of connectivity in the context of working memory in schizophrenia, and finally the use of intrinsic networks at rest or during a task to classify patients and controls.

Williamson and Allman provide a review of recent findings in schizophrenia in the context of an interaction of networks described as the salience network, the default mode network, and the executive control network and find them insufficient to explain symptoms or to differentiate schizophrenia from other illnesses. They propose an alternative framework which includes the dorsal anterior and posterior cingulate cortex, auditory cortex, and hippocampus and relate this to other networks related to mood disorders.

Mathalon and Ford review the search for neurobiological correlates of clinical symptoms and present a number of conceptual and methodological challenges which have hindered such work. Though there have been some successes, in large part studies of the brain-symptom relationship have been unsuccessful. They propose a variety of possible ways to better address the problem and continue to be optimistic that the link between brain structure and function and symptomatology is an important one.

Sui et al. provide a compelling review of multimodal fusion methods in schizophrenia. The merits of combining imaging modalities, each of which is limited and informs us of only a part of the information, is clear. The challenges have been many, for example the development of new models that can handle very high dimensional data. Dr. Sui provides a review of recent work in this area as well and reviews a range of fusion approaches from brain functional and structure to genetics and imaging. The advent of these new approaches bodes well for new ways to identifying important links between data which cannot be revealed by one or the other alone.

Liu et al. present a novel approach to combine functional imaging and whole genome polymorphism data. One of the challenges with analyzing genetic and imaging data is the number of variables is very high. Liu's approach provides a way to address this using a multivariate approach which can be used to guide the analysis using prior knowledge about which genetic factors or biological pathways are of primary interest while also allowing unanticipated genetic links to brain function to emerge from the data. Results reveal a link between functional changes in thalamus and cingulate with chromosome 7q21 and 5q35 which is compromised in the schizophrenia patients and clearly demonstrate the power of a hybrid approach to imaging genetics.

The next three articles are focused on one particular symptom, auditory visual hallucinations (AVH). In the first of three articles, Hoffman and Hampson review recent work on functional connectivity in AVH and suggest that the core mechanism for AVH involves a more complex functional loop rather than a single impaired pathway. Implicated regions include Wernicke's area, its right homolog, putamen, and left inferior frontal cortex. They also propose a number of important recommendations for future studies.

Diederen et al. provide a review of voice hearing in non-psychotic individuals, an important group to study to understand the underlying mechanisms of AVH in the absence of other psychiatric symptoms and medication. One observation they make is that individuals prone to hallucination may have an enhanced bias to auditory stimulation localized to the anterior cingulate regions. They also found evidence that decreased cerebral dominance, often found in schizophrenia, may not be directly related to AVH, again underscoring the importance of studying this population.

Along similar lines, Larøi discusses how AVH in patients differs from AVH in non-patients. He highlights several important aspects of these studies including the present of highly negative emotional context in the patient AVHs as well as the early onset of AVHs in the non-patients. Some key suggestions for future research are proposed as well.

Nygårdet al. focus on differences between patients and controls in functional connectivity across wide-spread networks identified with independent component analysis (ICA) including the default mode network and the so-called task-positive network located in regions subserving executive function. Their findings revealed differences in the degree to which patients up-regulated the default mode network and also a deficit in the down regulation of the anterior default mode network. The study of the dynamic interplay between different functionally connected networks is an emerging area and will undoubtedly play an important role in illuminating brain dysfunction in complex mental illnesses such as schizophrenia.

Repovš and Barch studies functional connectivity in the context of multiple working memory loads and patients, siblings, and healthy controls. They also evaluated the relationship among different networks as well as within networks. Interesting observations related to increases in some pairs of regions, e.g., default mode network and fronto-parietal connectivity while decreases in other pairs, e.g., cingulo-opercular and cerebellar at the lowest load level whereas the connectivity between the first pair was modulated by load. The second pair showed consistent differences in patients and their siblings and supports the view that altered functional connectivity in schizophrenia is a stable characteristic.

The final paper tackles the difficult problem of using imaging data to classify patients and controls. A unique aspect of this study is Du studies a wide number of intrinsic networks during both extended rest and task during an auditory oddball task. Using a novel analysis approach she obtains impressive results which suggest that despite the great interest in resting fMRI data for its ease of use and ability of patients to perform, a functional task which is relatively easy to perform may provide utility above and beyond rest fMRI in certain cases. Another key finding in this study is that classification information, though not the same across all networks, is wide-spread across the brain, and by incorporating multiple networks one can significantly improve performance.

In summary, the current collection of articles represents a wide range of topics related to cognitive impairment in schizophrenia and incorporates new approaches related to intrinsic networks identified at rest or during a task. The current selection of articles also shows how recent developments in structural and functional neuroimaging, may further advance our understanding of this devastating disorder. The more complete picture of these disorders provided by the study of functional and structural connectivity, combined with carefully evaluated tasks, and resting data will likely be important tools in future diagnostics and treatment evaluation.

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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 (lfMRI). 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 lfMRI, 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

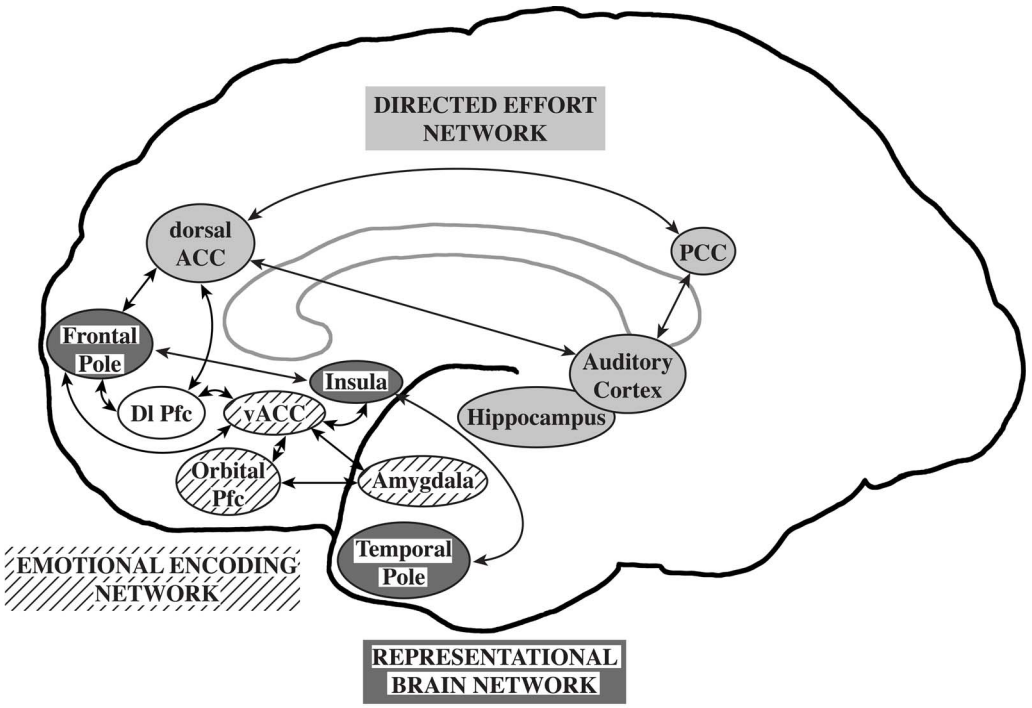

FIGURE 1 | The representational brain. The representational brain network (dark gray), proposed to underlie autism, includes the frontal pole, insula, and temporal pole. The directed effort network (light gray), proposed to underlie schizophrenia, includes the dorsal anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), auditory cortex, and hippocampus. The emotional encoding network (lined), proposed to underlie mood disorders, includes the orbital prefrontal cortex (Pfc), ventral anterior ACC, and amygdala. The directed effort and emotional encoding networks interact with the representational network and the dorsolateral prefrontal cortex (Dl Pfc, not shaded). Reprinted with permission from Williamson and Allman. *The Human Illnesses: Neuropsychiatric Disorders and the Nature of the Human Brain*. New York, NY: Oxford University Press, Copyright 2011.

(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, particularity 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; Kyriakopoulis 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). Salience 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

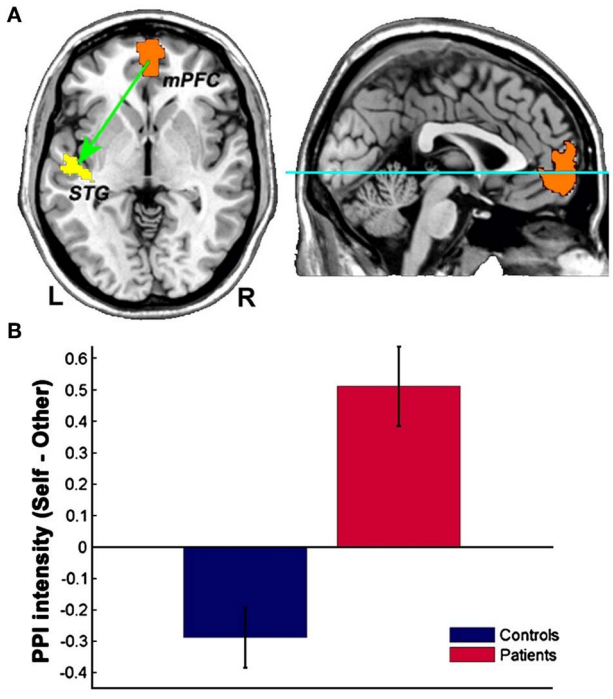

FIGURE 2 | Changes in functional connectivity with the medial prefrontal cortex in schizophrenia. The psychophysiological interaction (PPI) analysis revealed that functional connectivity from the medial prefrontal cortex to the left superior temporal gyrus is significantly modulated by source memory 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.

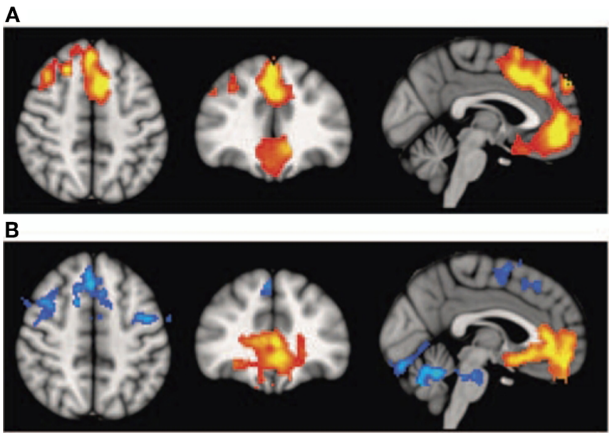

FIGURE 3 | Top panel: (A) Voxel-based morphometry (VBM) findings. Regions showing significant volume reduction thresholded at $p = 0.01$ in the schizophrenic patients are shown in orange. Bottom panel: **(B)** functional magnetic resonance imaging (fMRI) findings. Regions are shown where there were significant differences between patients and controls during performance of the n-back task (2-back versus baseline comparison), thesholded at $P = 0.01$. Blue indicates hypoactivation, that is, areas where controls activated significantly more than patients. Orange indicates areas where the schizophrenic patients showed failure to deactivate in comparison to controls. The right side of the images represents the left side of the brain. Reprinted from Pomarol-Clotet et al. (2010). Medial prefrontal cortex pathology in schizophrenia as revealed by convergent findings from multimodal imaging. *Mol. Psychiatry* 15, 823–830 with permission from Macmillan Publishers Limited.

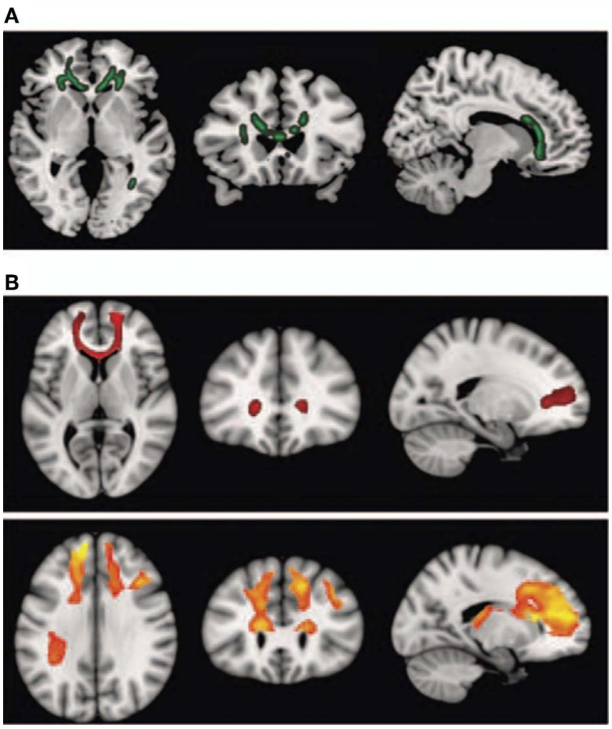

FIGURE 4 | Diffusion tensor imaging (DTI) findings. Top panel: **(A)** shows areas of significant fractional anisotropy (FA) reduction in the schizophrenic patients identified using Tract-based Spatial Statistics analysis thresholded at $p = 0.01$. Bottom panels **(B)** show areas of structural connectivity that differed significantly between the schizophrenic patients and controls, on the basis of the seed placed in the genu of the corpus callosum (upper, shown in red), and the seeds placed in the body of the corpus callosum, right and left (lower, shown in orange). A threshold of $p = 0.05$ corrected was used for this analysis. The right side of the image represents the left side of the brain. Reprinted from Pomarol-Clotet et al. (2010). Medial prefrontal cortex pathology in schizophrenia as revealed by convergent findings from multimodal imaging. *Mol. Psychiatry* 15, 823–830 with permission from Macmillan Publishers Limited.

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.

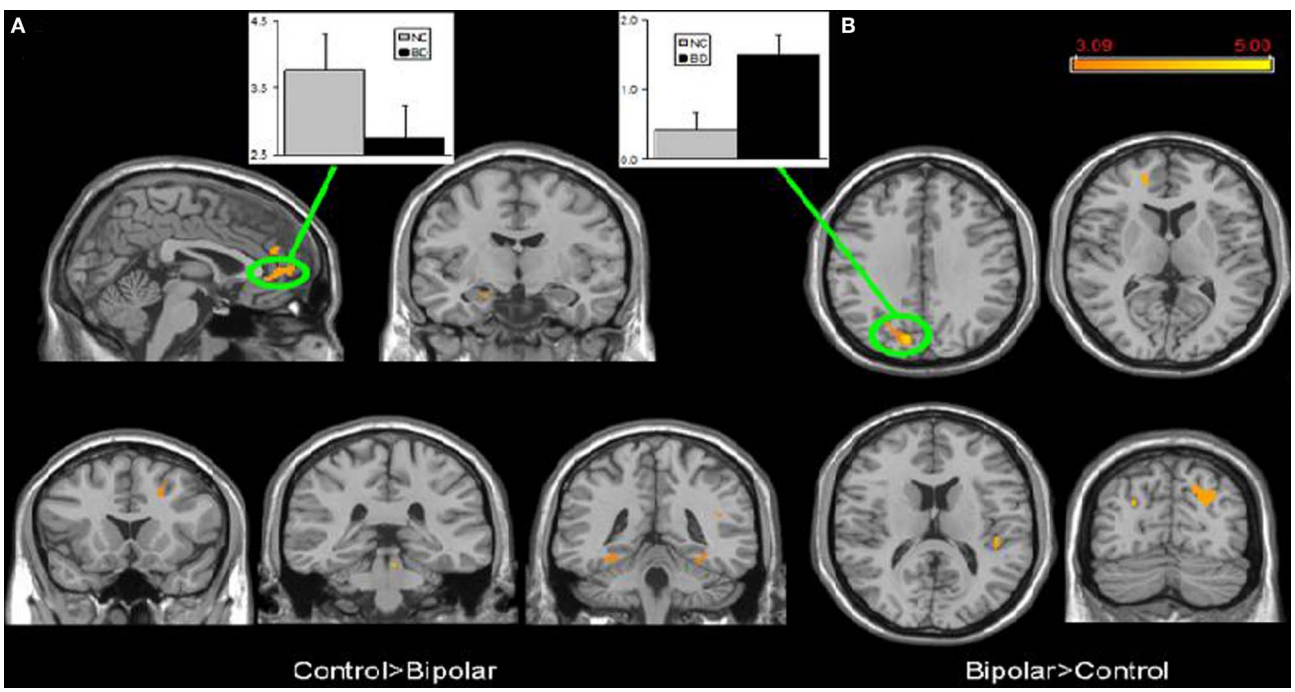

FIGURE 5 | Significant differences in the default mode network spatial extent between normal control and bipolar disorder subjects in whole brain analysis mapped onto parasagittal, coronal, and axial slices from a single subject's structural image in Talairach space; (A) Normal control > Bipolar disorder; (B) Bipolar disorder > Normal control. In each panel, average *z*-scores from a highlighted cluster are shown for normal control (gray) and bipolar disorder (black) groups, $p = 0.001$, 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.

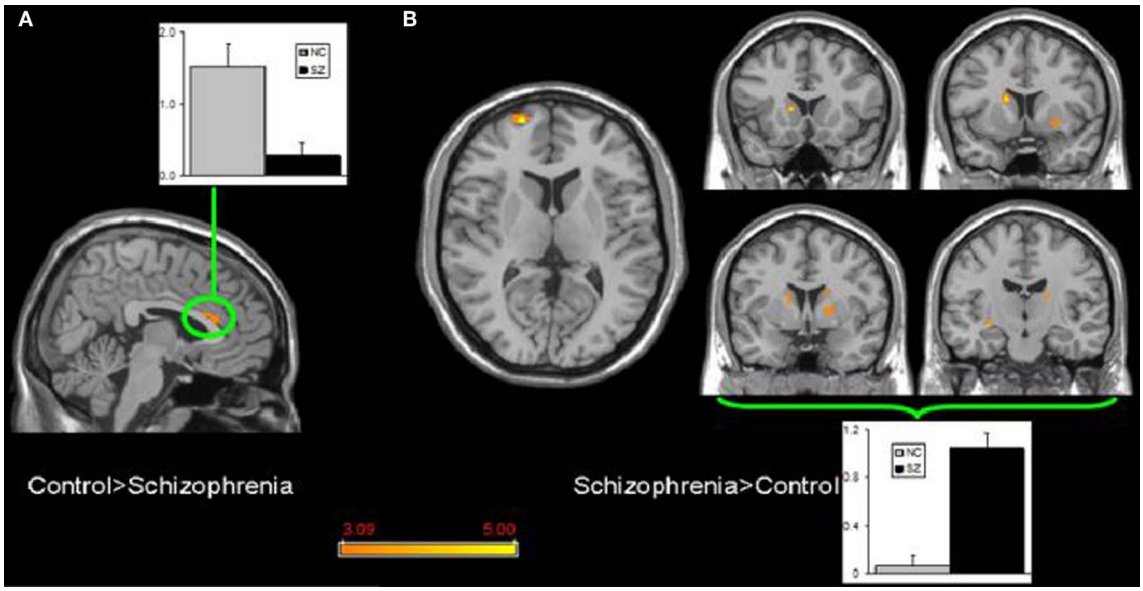

FIGURE 6 | Significant differences in the default mode network spatial extent between normal control and schizophrenia subjects in whole brain analysis mapped onto parasagittal, coronal, and axial slices from a single subject's structural image in Talairach space; (A) Normal control > Schizophrenia where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

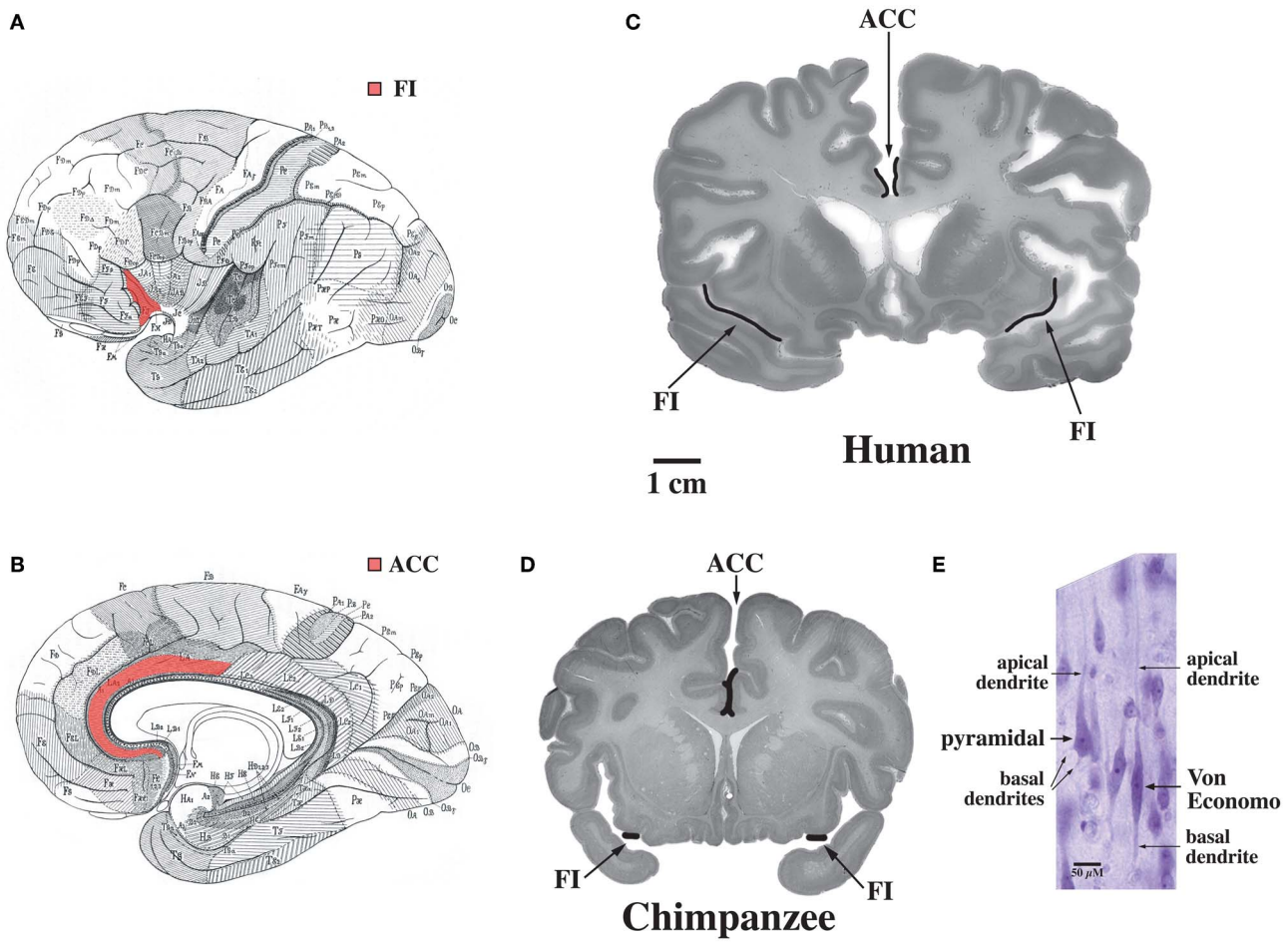

FIGURE 7 | Regions of the brain containing Von Economo neurons (VENs). (A) A lateral view of the brain, with fronto-insular cortex (FI) shown in red. **(B)** A medial view of the brain, with anterior cingulate cortex (ACC) shown in red. **(C)** FI and the spindle-cell-containing region of ACC indicated on coronal sections through a human brain (50-year-old female) and **(D)** a common chimpanzee brain (sections shown with the right hemisphere of the brain on the right of the figure). Note that FI is much larger in the human than in the chimpanzee. **(E)** A Von Economo neuron and a pyramidal neuron in layer 5 of FI. Both types of neuron have a single apical dendrite, but note that the VEN also has only a single basal dendrite, in contrast to the pyramidal neuron's multiple basal dendrites. Photomicrograph by the authors of a section from the 50-year-old human brain shown in part **(C)**. Reprinted from Allman et al. Intuition and autism: a possible role for Von Economo neurons. *Trends Cogn. Sci.* 9, 367–373, Copyright 2005, with permission from Elsevier.

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 adaptions 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; Yukie 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 Northoff 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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Neurobiology of schizophrenia: search for the elusive correlation with symptoms

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In the last half-century, human neuroscience methods provided a way to study schizophrenia *in vivo*, and established that it is associated with subtle abnormalities in brain structure and function. However, efforts to understand the neurobiological bases of the clinical symptoms that the diagnosis is based on have been largely unsuccessful. In this paper, we provide an overview of the conceptual and methodological obstacles that undermine efforts to link the severity of specific symptoms to specific neurobiological measures. These obstacles include small samples, questionable reliability and validity of measurements, medication confounds, failure to distinguish state and trait effects, correlation–causation ambiguity, and the absence of compelling animal models of specific symptoms to test mechanistic hypotheses derived from brain-symptom correlations. We conclude with recommendations to promote progress in establishing brain-symptom relationships.

Keywords: schizophrenia, positive symptoms, negative symptoms, neurobiology, correlation, reliability, validity, rating scales

Advances in neuroscience methods over the past 50 years have provided the means to study complex psychiatric disorders *in vivo*, firmly establishing that disorders once viewed as psychological reactions to stressful environments (particularly family environments) are associated with subtle abnormalities in brain structure and function. This historical transition toward reconceptualizing psychiatric disorders as brain disorders is exemplified by the paradigm shift that gave primacy to neurobiological and neurodevelopmental perspectives in understanding the etiopathology of schizophrenia. Despite the clinical heterogeneity of schizophrenia, a wide variety of neurobiological abnormalities have been replicated across clinical samples and research laboratories, providing some support for the neurobiological validity of the clinical criteria used to diagnose patients. However, efforts to understand the neurobiological bases of the clinical heterogeneity that schizophrenia comprises, mainly by correlating neurobiological measures with specific symptoms, have been largely unsuccessful. Indeed, it is fair to say that "inconsistency" has been the most consistent finding to emerge from such efforts. In this paper, we provide an overview of the myriad conceptual and methodological obstacles that undermine efforts to link the severity of specific symptoms to specific neurobiological measures, obstacles that ultimately impede progress toward elucidating the neurobiological mechanisms underlying these symptoms. We conclude with recommendations to promote progress in establishing brain-symptom relationships.

THE OBSTACLES

SMALL SAMPLES

Neurobiological studies that compare schizophrenia patients to healthy controls often include an analysis of symptom correlations within the patient group. The sample sizes needed to detect mean differences between patients and controls are typically smaller than the sample sizes needed to adequately power symptom correlation studies. The common practice of exploring symptom correlations within the relatively small patient samples employed in typical case-control studies often results in failures to detect significant associations between neurobiological measures and severity ratings of specific symptoms. However, in addition to insufficient power, correlations based on small sample sizes are also susceptible to spurious associations due to the influence that just a few data points can have on the small sample correlation coefficient. While the magnitude of correlations in small samples can be surprisingly large, leading some investigators to assume that the correlation is unlikely to have arisen by chance alone, 95% confidence intervals estimated for small sample correlations are very wide, reflecting the high level of uncertainty about where the true correlation actually lies (**Figure 1**).

The problem of small samples is exacerbated by the need to control the type-I error rate for the number of correlations tested, leading to very stringent significance thresholds. However, it is not uncommon for studies that report symptom correlations to forego correction for multiple tests by describing the correlational analyses as "exploratory." The result is that the schizophrenia research literature is replete with inconsistent findings of "significant" correlations with various symptom dimensions based on small patients samples. It is unclear whether these small sample correlations actually move the field forward, or whether they primarily clutter the literature with spurious findings.

What constitutes a small sample? Certainly sample sizes of 30 or less seem small given the need to represent the full range of symptom variation in the patient sample. Sample sizes of

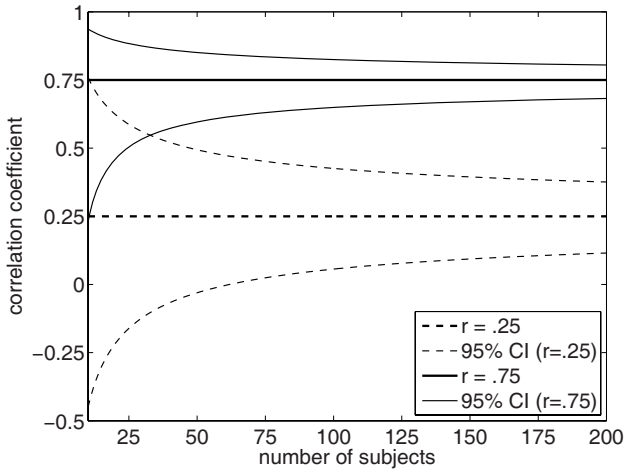

FIGURE 1 | This figure shows the 95% confidence intervals for two Pearson product-moment correlation coefficient values, $r = 0.25$ and $r = 0.75$, as a function of sample size. Note the wide confidence intervals when correlations are based on small sample sizes, particularly when $n < 50$ subjects.

at least 50 patients seem better suited for robust detection of symptom correlations, but such sample sizes are uncommon for neurobiological studies of schizophrenia from individual laboratories.

QUESTIONABLE RELIABILITY AND VALIDITY OF MEASUREMENTS

Implicit in the assessment of correlations between clinical symptom measures and neurobiological measures is the assumption that both measures possess sufficient reliability and validity to support a meaningful examination of their inter-relationship. However, this assumption is seldom verified empirically. On the clinical side, symptoms are typically quantified using interview-based rating scales such as the Positive and Negative Symptom Scale (PANSS; Kay et al., 1987), Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983), or Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962, 1988). These scales assess the severity of a specific symptom domain with a single item or a few items, failing to adhere to the psychometric principle that averaging over many items enhances the reliability of psychological construct measurement (Wiggins, 1980; Anastasi, 1982). This sharply contrasts with the typical multi-item approach to measurement taken by psychologists when developing instruments to assess cognitive abilities, personality traits, or other complex psychological constructs.

The problem of unreliability of clinical symptom measurements is exacerbated by the fact that symptoms are typically assessed by interviewers making severity ratings based on semi-structured patient interviews. While this calls for considerable skill and judgment on the part of the interviewer, inter-rater reliability is seldom assessed and reported in papers that examine symptom correlations with neurobiological measures. Moreover, although averaging the judgments of multiple raters together can enhance the reliability of measurement, relative to the use of ratings from a single rater (Wiggins, 1980; Anastasi, 1982), this approach is rarely used in schizophrenia research. Even when inter-rater reliability is assessed and reported in clinical studies, it is typically assessed by having two or more raters rate the same set of patient interviews, often derived from a videotape library of prior interviews. This approach inflates the true reliability of interview-based ratings by failing to consider the unreliability introduced by variation across interviewers in their skill and technique in eliciting symptom information from patients. Whether the ratings from two independent raters conducting separate patient interviews are reliable is typically not examined in schizophrenia studies, obscuring what may be a major source of measurement error in the assessment of symptom severity.

In addition to the variation introduced by different interviewers conducting clinical ratings, unreliability also arises from inconsistencies in the way patients endorse and describe specific symptoms, which may interact with the specific interviewer but also with the particular mental state of the patient. Again, the degree to which the reliability of symptom ratings is degraded by patient inconsistencies in reporting is seldom quantified in schizophrenia studies, leading to inflated estimates of the true reliability of symptom ratings. The need for reliable symptom measurements when correlating symptom ratings with neurobiological measures is underscored by the well-known principle that reliability sets the upper limit on validity; that is, assuming that measurement errors are random, a clinical symptom measure cannot be expected to correlate more highly with a neurobiological measure than it correlates with itself (Wiggins, 1980; Anastasi, 1982; de Klerk, 2008).

Aside from reliability concerns in connection with interview-based symptom rating scales, there is good reason to question whether these ratings are valid reflections of the specific symptom severities they are intended to capture. There are a number of threats to validity of clinical ratings that are seldom discussed in the schizophrenia research literature. For example, schizophrenia patients may have difficulty providing accurate information about their symptoms, including their frequency, duration, severity, and impact on their lives. These difficulties may arise from a lack of insight, deficits in self-reflection and self-monitoring, poor memory when trying to recount the frequency and severity of symptoms that have occurred over prior weeks or months, guardedness and paranoia leading to under-reporting of symptoms, and desire to please the interviewer leading to over- or under-reporting of symptoms. While alternatives to interview-based retrospective self-reports of symptoms have been described in the literature, including experience sampling methods (Csikszentmihalyi and Larson, 1987; Ben-Zeev et al., 2011; Swendsen et al., 2011; Oorschot et al., 2012) where patients report symptoms in real-time in response to a randomly delivered signal (e.g., pager or phone call) or record symptoms in a diary on a daily basis, these approaches are seldom used in neurobiological studies of schizophrenia. Undoubtedly, such measurements are time consuming and challenging to obtain, but they may provide a more valid picture of the severity of specific symptoms over a defined time period than can be obtained from retrospective reports elicited during an interview.

Of course, the same concerns about measurement reliability and validity apply to the neurobiological measurements that are correlated with symptom measures in schizophrenia studies. Typically there is no attempt to establish that neurobiological measures derived from neuroimaging or electrophysiological recordings are reliable over time. Yet, this is often an implicit assumption when correlating such measures with ratings that retrospectively integrate symptom severity information over the past week, the past month, or the patient's lifetime. Unreliability of neurobiological measures over relatively short time periods can be expected to attenuate the observed correlations between these measures and symptom severity ratings.

MEDICATION AND TREATMENT RESPONSE CONFOUNDS CLINICAL SEVERITY RATINGS

Medication status is another factor that introduces noise into the assessment of correlations between symptom severity and neurobiological measures. In most neurobiological studies of schizophrenia, patients are taking stable doses of anti-psychotic medication (and other medications such as antidepressants, mood stabilizers, and anxiolytics) at the time of testing. As a result, ratings of symptom severity reflect variation across patients in the responsiveness of symptoms to treatment, rather than just the variation across patients in the primary pathophysiological processes underlying the severity of specific symptoms. Thus, taking auditory hallucinations as an example, it may be that the neurobiological abnormalities underlying auditory hallucinations will correlate with the severity of untreated hallucinations but not with the severity of residual hallucinations present during chronic anti-psychotic treatment.

In addition, to the extent that patients with more severe or treatment-resistant symptoms receive higher doses of medication, dose-related medication effects can confound the correlation between a neurobiological measure and symptom ratings, potentially introducing spurious correlations between them. While the confounding effects of medication and variation in treatment response can be addressed by studying unmedicated patients, it is generally considered unethical to subject patients to a drug washout solely for the purpose of studying them in an unmedicated state in neurobiological research protocols.

STATE VS. TRAIT CONFUSION

The natural history of schizophrenia involves fluctuations in the severity of symptoms, particularly positive symptoms, over the illness course. While these fluctuations can be influenced by environmental stressors, they may also be due to pathophysiological fluctuations that have yet to be elucidated. In any case, patients also exhibit trait-like individual differences in symptom severity, with some patients having milder forms of the illness and others being more severely affected. Clinical state fluctuations over time are superimposed on these trait-like individual differences, with each patient fluctuating around his or her own mean level of severity for any given symptom.

Some neurobiological measures, particularly those that reflect brain function and potentially the dynamic neural mechanisms underlying specific symptoms (e.g., ERP or fMRI activation measures), are also likely to show trait-like individual differences and state-related fluctuations over time around each patient's own mean for that measure. In cross-sectional studies that attempt to correlate neurobiological measures with symptom ratings, the trait- and state-related contributions to a patient's symptom severity and neurobiological function are confounded, potentially obscuring a true correlation between state-related changes in symptom severity and neurobiological function. Detection of such correlations requires multi-wave longitudinal assessments in order to model the covariation between a neurobiological measure and symptom severity within each subject without the confound of trait-like individual differences. We successfully demonstrated such an approach in a study that showed fluctuations in the P300 component of the auditory ERP to correlate with positive symptom fluctuations within patients over time (Mathalon et al., 2000). This relationship was not evident in a cross-sectional analysis that attempted to correlate the between-subject differences in P300 and positive symptom severity at a single time point.

Other neurobiological measures that reflect more static characteristics of the brain may not be sensitive to clinical state fluctuations but rather may underlie trait-like individual differences between patients in symptom severity. For example, allelic variation in particular genes may be correlated with trait-like individual differences in the propensity to hallucinate or with the mean severity of hallucinations over the illness course. Such correlations may be significantly attenuated in cross-sectional study designs because the symptom ratings are excessively influenced by the patient's current clinical state. Yet the correlation may become evident if symptom ratings are averaged over multiple occasions over the illness course in order to increase their sensitivity to trait-like individual differences. Averaging over multiple measurement occasions increases the temporal reliability of a symptom measure as predicted by the well-known Spearman–Brown prophecy formula from classical test theory. In practice, the benefit of this approach was demonstrated by Epstein and colleagues in connection with the validation of personality trait measures as predictors of specific behaviors (Epstein, 1984, 1997; Epstein and O'Brien, 1985; Epstein et al., 1996). We similarly showed enhanced detection of the correlation between negative symptoms and P300 amplitude by averaging each of the measures over multiple measurement occasions over the illness course (Mathalon et al., 2000). Similarly, we demonstrated enhanced detection of correlations between progressive gray matter decline in schizophrenia and positive symptom severity by averaging the symptom severity over the baseline and follow-up assessments (Mathalon et al., 2001). In general, studies that examine symptom correlations with neurobiological measures in the schizophrenia literature do not make explicit whether the neurobiological measures posited to underlie specific symptoms should show state-related, or trait-related, covariation with symptom severity. The failure to make this distinction leads to sub-optimal study designs for testing hypotheses about brain-symptom relationships.

CORRELATION–CAUSATION LIMITATIONS

A significant limitation of clinical research in general, and schizophrenia research in particular, is that we are generally limited to studying pre-existing symptoms and brain abnormalities. Our inability to experimentally manipulate brain mechanisms to

modulate specific symptoms leads us to rely exclusively on correlational data to evaluate mechanistic models of specific symptoms. Since correlations cannot prove causation, even the demonstration of robust and replicable correlations between a neurobiological measure and symptom severity cannot definitively establish that there is a causal relationship.

THIRD VARIABLES

Related to the correlation–causation limitation of clinical research studies is the potential for correlations between specific neurobiological measures and specific symptoms to be mediated by "third variables." Often these third variables are not measured in the study, obscuring their role in producing the observed brain-symptom correlation. Examples may include exposures to environmental toxins, abnormalities of specific peptides or proteins, or other pathophysiological mechanisms that have yet to be elucidated. Such variables may give rise to both the measured neurobiological abnormality and the clinical symptom being assessed, and the resulting correlation between the two may have little to do with any underlying causal relationship between them. Moreover, to the extent that the severity of apparently distinct symptoms such as hallucinations and persecutory delusions are correlated, the apparent relationship between a neurobiological measure and one symptom (e.g., hallucinations) may be mediated by its relationship with the correlated symptom (e.g., delusions). Indeed, it remains likely that the actual causal pathophysiological mechanisms that give rise to a number of measured neurobiological abnormalities and a wide range of clinical symptoms, as well as observed correlations between them, have yet to be discovered. This problem fundamentally limits the ability of correlations between neurobiological measures and symptom severity to definitively identify the neurobiological causes of specific symptoms in schizophrenia.

MISTAKEN *A PRIORI* HYPOTHESES

A minority of clinical symptom correlation studies in schizophrenia are motivated by specific mechanistic hypotheses about how abnormalities of a specific neurobiological measure should be selectively related to specific symptoms. While hypothesis driven analyses are generally considered to have more scientific value than exploratory "fishing expeditions," conceptually reasonable hypotheses may nonetheless be incorrect. There are numerous examples of this in the schizophrenia literature. Working memory deficits, which compromise the ability to hold information online for short periods of time, have been hypothesized to contribute to formal thought disorder (i.e., disorganized thought process) in schizophrenia (Goldman-Rakic, 1994, 1999), yet relationships between them have not generally been found (but see Perlstein et al., 2001). Similarly, abnormalities in semantic network activations, as reflected by the N400 ERP component, might reasonably be predicted to underlie formal thought disorder, yet often it is delusional thinking rather than thought disorder that correlates with N400 (Debruille et al., 2007). The error-related negativity (ERN), an ERP component elicited by commission errors in choice-response tasks, has been linked to reward processing and reward prediction errors (Goldman-Rakic, 1999; Holroyd and Coles, 2002). Based on this, it is reasonable to predict that ERN abnormalities in schizophrenia should be related to negative symptoms, particularly motivational impairments and anhedonia (Morris et al., 2011). However, reduced ERN amplitude has instead generally been associated with increased positive symptom severity (Mathalon et al., 2002) or the paranoid subtype of schizophrenia in several studies (Kopp and Rist, 1999; Mathalon et al., 2002). Thus, sometimes *a priori* theoretical models may lead investigators to make the wrong prediction about which symptoms will correlate with a neurobiological measure. While this argues in favor of data-driven exploratory analyses of brain-symptom correlations, the down side of such explorations is the inflated type-I error rate associated with statistical testing of large numbers of correlations.

ABSENCE OF COMPELLING ANIMAL MODELS FOR SPECIFIC SYMPTOMS

A potentially powerful approach to corroborating specific symptom correlations with neurobiological measures from a mechanistic perspective is to experimentally manipulate the neurobiological measure to induce the symptom in an animal model. Unfortunately, despite the fact that some investigators have speculated that psychotic like symptoms can be observed in non-human primates, there are no compelling animal models for the cardinal symptoms of schizophrenia including auditory hallucinations, delusions, formal thought disorder, and negative symptoms. Relative to other medical diseases that have animal models (e.g., diabetes), the schizophrenia field is hampered by the fact that the symptoms are mainly evident via self-report and language-based communication, neither of which are readily studied in non-human primates or rodents. This fundamentally limits our ability to get scientific traction on the problem of elucidating the neurobiological basis of specific symptoms in schizophrenia. It should be noted that animal models have been developed to study neurobiological measures known to be abnormal in patients in schizophrenia, including ERP components such as mismatch negativity (Javitt et al., 1996; Ehrlichman et al., 2009; Amann et al., 2010) and P50 sensory gating (Freedman et al., 1996; Metzger et al., 2007; Amann et al., 2010). However, these approaches do not overcome the challenges of establishing homologies between animal models and specific clinical symptoms.

POTENTIAL SOLUTIONS AND RECOMMENDATIONS

LARGER SAMPLES AND BETTER MEASUREMENTS

Efforts to find robust correlations between specific symptoms and specific neurobiological measures in schizophrenia would likely achieve more success if such studies employed larger sample sizes where confidence intervals are tighter and spurious correlations are less likely. Inspection of the confidence interval plots shown in **Figure 1** suggest that the benefits of larger samples for detecting correlations with confidence starts to diminish after somewhere between 50 and 100 subjects (see **Figure 1**). In addition, the field needs to make advances in the measurement of symptoms, going beyond the retrospective interview-based ratings of one or a few items that typify the approach taken in current studies. Examples of such approaches include multi-item ratings scales for hallucinations like the psychotic symptom rating scale (PSYRATS; Drake et al., 2007), real-time event sampling to reduce the reliance on patient's retrospective accounts of their symptoms, and assessments of symptoms at multiple time points over the illness course

to facilitate the distinction between trait- and state-related variation in symptom severity. Finally, greater emphasis needs to be placed on accurate estimation of the reliability of symptom measurements, as well as the reliability of the neurobiological measures that are correlated with symptom severity.

STUDIES OF FIRST-EPISODE MEDICATION-NAIVE PATIENTS AND CHRONIC PATIENTS WHO DO NOT ADHERE TO MEDICATION REGIMENS

Studies of medication naïve first-episode patients is a potentially useful strategy for capturing variation in primary symptom severity with the confounding effects of medication, but such patients are difficult to recruit and the duration of time that medication can be ethically withheld is fairly limited. Moreover, to the extent that schizophrenia involves a progressive pathophysiology over the illness course, symptom correlations present at the onset of illness may not hold for chronic patients. That symptoms may depend on the stage of illness is supported by studies that suggest that positive symptoms become less severe and negative symptoms more prominent in the later stages of schizophrenia (McGlashan, 1988; McGlashan and Fenton, 1992).

In addition, studying samples of schizophrenia patients who have transiently discontinued their medication or who choose not to take medication is another approach to capturing symptom variation in the absence of medication confounds. However, this approach may not yield symptom correlations that generalize to the entire population of schizophrenia patients, particularly to the extent that chronic patients who can live independently in the community without medication may not be representative of schizophrenia patients in general.

OVERCOMING THE CORRELATION–CAUSATION LIMITATION OF CLINICAL RESEARCH STUDIES

One strategy that attempts to overcome the limitations of correlational brain-symptom data in clinical research studies is to use pharmacological challenges with agents that affect specific neuroreceptors in order to transiently exacerbate symptoms in patients, or to transiently induce schizophrenia-like symptoms in healthy volunteers. This strategy is exemplified by the use of the NMDA-receptor antagonist, ketamine, in challenge studies with patients (Lahti et al., 1995) and healthy volunteers (Krystal et al., 1994, 2003; Adler et al., 1999; Umbricht et al., 2000; Moore et al., 2011; Neill et al., 2011), to test the hypothesis that NMDA-receptor hypofunction contributes to both clinical symptoms and neurocognitive deficits in schizophrenia.

Another promising approach to overcoming the correlation–causation conundrum that is still in its early stages of development is the use of transcranial magnetic stimulation (TMS) to transiently perturb specific brain regions and circuits (Slotema et al., 2010). While repetitive TMS has already been studied as a potential treatment for auditory hallucinations (Hoffman et al., 2000), the possibility of using TMS targeted at specific brain regions to transiently increase or decrease specific symptoms in order to provide evidence for the causal role of that brain region in producing or modulating the symptom remains largely unexplored. Nonetheless, both the pharmacological probe and the TMS probe approach to establishing causal connections between brain function and specific symptoms have some conceptual limitations. In particular, even if manipulating brain function with these methods can reproduce schizophrenia-like symptoms, this does not preclude the possibility that distinctly different pathophysiological mechanisms give rise to these symptoms in schizophrenia.

EXTENDING SYMPTOM DIMENSIONS ACROSS TRADITIONAL DIAGNOSTIC BOUNDARIES

To the extent that some symptoms of schizophrenia are also evident in other neuropsychiatric disorders, studying these symptoms across disorders can provide some leverage against confounds that tend to be more specific to the schizophrenia spectrum. For example, auditory hallucinations can occur in bipolar mania or depression when psychosis accompanies these mood states. Bipolar patients may not have the chronic exposure to anti-psychotic medication typical of schizophrenia, instead being treated with drugs like lithium, valproic acid, and antidepressants. This provides some opportunities to examine symptom correlations with neurobiological measures in bipolar disorder without the confound of dopamine D2 blockade associated with anti-psychotic drugs. Moreover, bipolar patients do not tend to exhibit the negative symptoms or severe functional impairment characteristic of schizophrenia, allowing further dissociation of what tend to be correlated impairments in schizophrenia. Indeed, linking symptoms to brain circuits across traditional diagnostic boundaries has been identified as a major research initiative by NIMH, the so-called Research Domain Criteria (RDoC) initiative. This approach may provide a greater range of variability for specific symptoms and neurobiological abnormalities that can enhance the likelihood of finding significant covariation between them.

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A selective review of multimodal fusion methods in schizophrenia

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Schizophrenia (SZ) is one of the most cryptic and costly mental disorders in terms of human suffering and societal expenditure (van Os and Kapur, 2009). Though strong evidence for functional, structural, and genetic abnormalities associated with this disease exists, there is yet no replicable finding which has proven accurate enough to be useful in clinical decision making (Fornito et al., 2009), and its diagnosis relies primarily upon symptom assessment (Williams et al., 2010a). It is likely in part that the lack of consistent neuroimaging findings is because most models favor only one data type or do not combine data from different imaging modalities effectively, thus missing potentially important differences which are only partially detected by each modality (Calhoun et al., 2006a). It is becoming increasingly clear that multimodal fusion, a technique which takes advantage of the fact that each modality provides a limited view of the brain/gene and may uncover hidden relationships, is an important tool to help unravel the black box of schizophrenia. In this review paper, we survey a number of multimodal fusion applications which enable us to study the schizophrenia macro-connectome, including brain functional, structural, and genetic aspects and may help us understand the disorder in a more comprehensive and integrated manner. We also provide a table that characterizes these applications by the methods used and compare these methods in detail, especially for multivariate models, which may serve as a valuable reference that helps readers select an appropriate method based on a given research question.

Keywords: multimodal fusion, schizophrenia, MRI, DTI, EEG, SNP, ICA, CCA

BRIEF INTRODUCTION TO SCHIZOPHRENIA

Schizophrenia is a chronic, disabling mental disorder diagnosed on the basis of a constellation of clinical psychiatric symptoms and longitudinal course. The disease impairs multiple cognitive domains including memory, attention, and executive function (Heinrichs and Zakzanis, 1998). Although the causes and mechanisms of schizophrenia are still unclear, a hypothesis of neural network "disconnection" has been proposed (Friston and Frith, 1995). This hypothesis proposes that schizophrenia arises from dysfunctional integration of a distributed network of brain regions or a misconnection of neural circuitry leading to an impairment in the smooth coordination of mental processes, sometimes described as "cognitive dysmetria" (Andreasen et al., 1998). A number of studies have been published which have tried to delineate the underlying neural mechanisms of schizophrenia using functional magnetic resonance imaging (fMRI; Pearlson, 1997; Loeber et al., 1999; Curtis et al., 2001; McIntosh et al., 2008b; Yu et al., 2011a), structural MRI (sMRI; Giuliani et al., 2005; Strasser et al., 2005; Douaud et al., 2007), diffusion tensor imaging (DTI; McIntosh et al., 2008a; Kubicki et al., 2009; Sussmann et al., 2009), and genetics (Bahn, 2002; Williams et al., 2010b; Ripke et al., 2011). For example, in fMRI studies, deficits in dorsolateral prefrontal cortex (DLPFC; Hamilton et al., 2009) and the temporal lobe (Calhoun et al., 2008) have often been implicated in schizophrenia. In addition, DTI studies have found reduced integrity of the anterior limb of the internal capsule, uncinate fasciculus (UF), and anterior thalamic radiation (ATR) regions in schizophrenia (Kubicki et al., 2005b; Bellani et al., 2009; Sussmann et al., 2009). Finally, in genome wide association (GWAS) studies (Bahn, 2002; Shifman et al., 2004; Williams et al., 2009; Ripke et al., 2011), gene expression alterations have been reported in CACNA1C, ANK3, MIR137, and DISC1 recently. Given the breadth of findings across modalities, it is natural to evaluate the inter-relationship among them within a larger context.

WHY MULTIMODAL

Recently, collecting multiple types of brain data from the same individual using various non-invasive imaging techniques [MRI, DTI, electro-encephalography (EEG), MEG, etc.] has become common practice. Each imaging technique provides a different view of brain function or structure. For example, fMRI measures the hemodynamic response related to neural activity in the brain dynamically; sMRI provides information about the tissue type of the brain [gray matter (GM), white matter (WM), cerebrospinal

fluid (CSF)]. DTI can additionally provide information on structural connectivity among brain networks. Another useful measure of brain function is EEG, which measures brain electrical activity with higher temporal resolution than fMRI (and lower spatial resolution). Typically these data are analyzed separately; however separate analyses do not enable the examination of the joint information between the modalities. In addition, focusing on a single modality in brain connectivity estimation can sometimes lead to contradicting conclusions (Plis et al., 2011).

Based on many previous findings in brain connectivity (Olesen et al., 2003; Rykhlevskaia et al., 2008; Camara et al., 2010; Yu et al., 2011b), it is plausible to assume covariation between brain function and structure. In addition, approximately 80% of total assayed genes display some cellular expression in brain (Lein et al., 2007). Therefore, it is reasonable to assume that these very diverse data may share certain underlying contributions to the etiopathology of brain disorders such as schizophrenia and jointly analyzing multimodal data may uncover previously hidden relationships that can only be partially detected in each modality alone. A motivating example is shown in **Figure 1**, in which a fiber bundle provides input to a distant location in varying degrees in two participants whose particular single nucleotide polymorphisms (SNPs) also differ, thus fMRI activity is different at the output location and possibly in functional connectivity (fMRI activity at the input is unaffected). The interactions between modalities (**Figure 1B**) would not be revealed by traditional separate analysis whereas a joint analysis (**Figure 1C**) would detect the underlying associations.

A key motivation for multimodal fusion is to take advantage of the cross-information provided by multiple imaging techniques, which in turn can be useful for identifying dysfunctional regions or potential biomarkers for many diseases. Basically, multimodal fusion refers to the use of a common symmetric model that explains different sorts of data (Friston, 2009). This is a complicated endeavor, and can generate results that are not obtainable using traditional approaches which focus upon a single data type or processing multiple datasets individually. However, in the real world, challenges often come from the fact that conclusions need to be drawn from high dimensional and noisy brain imaging data from only a limited number of subjects. Hence efficient and appropriate methods should be developed and chosen carefully.

In addition, multimodal brain imaging data has shown increasing utility in answering both scientifically interesting and clinically relevant questions. As well as providing the conceptual glue to bind together data from multiple types or levels of analysis, the related computational methods are also valuable for clinical research on the mechanisms of disease progression. For example, researchers often look for reliable relationships between few summary values from each modality, and certain behavioral dependent variables, e.g., the symptom scores of the patients with disorders, which may allow assessment of functional links between brain dynamics and human cognitive process. The incorporation of behavioral/cognitive data into multimodal fusion analysis which take the entire data into account and are not limited to a single region will not only improve our physiological understanding of brain diseases, but also provide insight into the neural bases of these human cognition or behavior (Makeig et al., 2009).

For schizophrenia, though strong evidences exist for functional, structural, and genetic abnormalities in each single-modality analysis, there is still lack of a diagnostic "gold standard" which is specific and sensitive enough to guide clinical decisions (Fornito et al., 2009). Even though GWAS studies have identified several risk genes that may influence brain functions affected in schizophrenia, they have not illuminated the etiology of the disease as they were perhaps anticipated to (Ripke et al., 2011; Williams et al., 2011). Therefore, it is likely at least in part, that a lack of consistent findings results from most studies favoring only one data type or not combining modalities in an integrated manner (Calhoun et al., 2006a).

Next, we will review several multimodal fusion applications in schizophrenia applied to different data types. Note that many fusion applications rely on studying correlations between highly distilled measures, e.g., from small regions of interest (Tregellas et al., 2007; Bates et al., 2009; Foucher et al., 2011). However the applications we reviewed mostly examine more complete relationships among the data types based on multivariate methods. Finally,

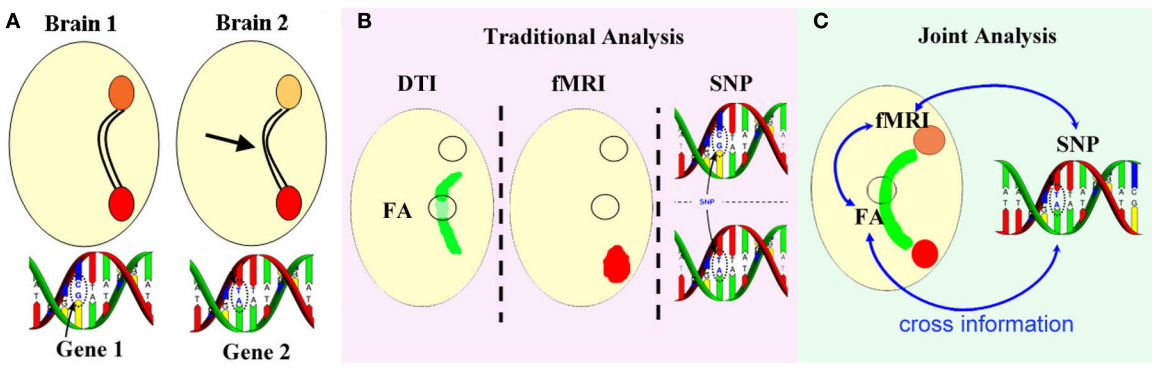


FIGURE 1 | Motivating example for multimodal joint analysis. (A) Fiber bundle [fractional anisotropy (FA) from DTI] provides varied input to a distant region in two participants whose particular SNPs also differ, thus fMRI activity is different at the output location (orange circles) and possibly in functional connectivity, while fMRI activity at the input (red circles) is unaffected. Traditional separate analysis of each modality **(B)** would not reveal such modal interactions, whereas a joint analysis **(C)** may detect the underlying associations.

we classify these applications based on the fusion models used, in order to provide a framework for selection of methods in future applications.

MULTIMODAL FUSION APPLICATIONS IN SCHIZOPHRENIA

FUNCTION–FUNCTION

Functional magnetic resonance imaging–EEG (ERP)

The combination of fMRI and EEG is the most frequently used brain imaging fusion examples. Because it is believed that the spatial precision of fMRI can be complemented by the temporal precision of EEG (Friston, 2009) so that the neurovascular coupling mechanism can capture both neuronal and hemodynamic activity as two important components. One approach used for fMRI–EEG fusion is to constrain one modality with another, as reported in Dale and Halgren (2001), Eichele et al. (2005), Henson et al. (2010). While these are powerful techniques, a common limitation is that the potentially unrealistic assumptions of a fundamentally different nature than the known modality are imposed on the constrained data. For example, constraining EEG sources to lie within fMRI activated regions makes the implicit assumption that both signals have the same origin, or if present should be at least correlated, which is not always true. The fMRI signal is undoubtedly related to changes in blood follow, but it is by no means related in a simple ways to neuronal activity. Furthermore, transient EEG activity might not induce a detectable hemodynamic effect, and intense neuronal activity that is desynchronized may lead to strong hemodynamic effects with on detectable average electrical activity (Jbabdi, 2009). By contrast, data-driven fusion methods are attractive for exploring data sets more fully, as they do not require prior hypotheses about the connection of interest.

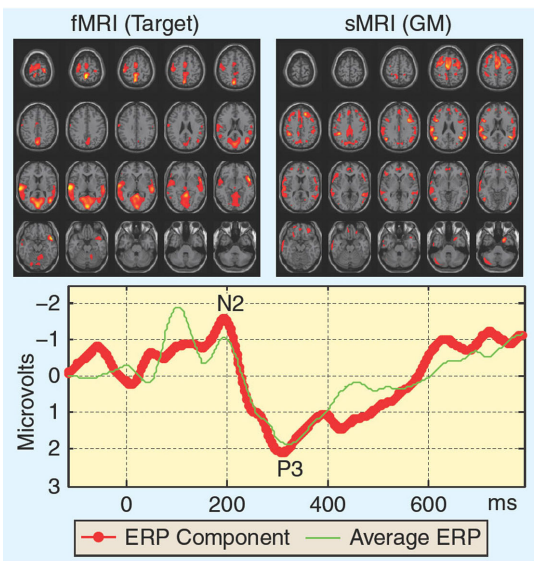
Calhoun et al. (2006b, 2011) first proposed a joint independent component analysis (jICA) model (which assumes that two or more modalities share the same mixing matrix) to fuse together fMRI and EEG data, and aimed to identify specific differences in the neuronal chronometry of target detection for chronic schizophrenia patients compared to healthy controls (HC). One group-discriminative joint component was found via two-sample t-test ($p < 0.0001$), showing a clear difference in fMRI at bilateral fronto-temporal regions and in the event-related potentials (ERPs) during the N2–P3 latency range (ERPs are labeled based on their ordinal position following the stimulus onset, e.g., P3 for the third positive peak or N2 for the second negative peak). Note that both the hemodynamic and electro-physiologic phenomena were jointly expressed in this source, which have been previously implicated in schizophrenia, but no prior study had showed that changes in these two modalities were linked.

Correa et al. (2010b) also tried to differentiate schizophrenia from controls by applying multimodal canonical correlation analysis (mCCA) to fMRI–EEG data during performance of an auditory oddball (AOD) task (Kiehl and Liddle, 2001). Significant group differences were found in the bilateral temporal lobe/middle anterior cingulate region in fMRI, associated with the N2 and P3 peak in EEG. Multimodal CCA allows a different mixing matrix for each modality and is able to find a transformed coordinate system that maximizes inter-subject covariation across two or more data sets (Li et al., 2009). As shown in **Figure 2**, a set of linked components derived from a three-way fusion of sMRI, fMRI, and EEG were detected (Correa et al., 2010a), which significantly discriminate schizophrenia patients from controls. On examining the inter-subject modulation in conjunction with the spatial and temporal components, the results imply that patients with schizophrenia have less functional activity and less GM in the motor and temporal areas and also in part of the ERP N2/P3 complex. The comparison of t-tests for three modality (fMRI, sMRI, and EEG) versus two modality (fMRI and sMRI) analyses for this set of components is also listed, showing that the three-way analysis was more significant than a two- or one-way analysis, which further validates our motivation for multimodal fusion.

STRUCTURE–STRUCTURE

Gray matter–white matter

Using joint ICA, Xu et al. also identified four joint sources that were significantly associated with schizophrenia. The linked GM–WM regions identified in each of the joint sources included: (1) temporal – corpus callosum, (2) occipital/frontal – inferior fronto-occipital fasciculus, (3) frontal/parietal/occipital/temporal –superior longitudinal fasciculus, and (4) parietal/frontal – thalamus (Xu et al., 2009), which include a large number of brain regional networks and reflecting the widespread nature of the disease. A complex pattern of regional increases and decreases in schizophrenia were reflected. For example, for joint source 1, linkage between less GM in temporal lobe and the less WM in corpus callosum is interesting and may be related to the posterior corpus



MODALITIES	THREE MODALITIES		TWO MODALITIES	
	t	α	t	α
fMRI	3.45	0.002	2.17	0.038
sMRI	2.86	0.001	2.20	0.034
EEG	3.61	0.007	–	–

FIGURE 2 | Functional magnetic resonance imaging/EEG/sMRI fusion by mCCA from Correa et al. (2010a): a set of associated components estimated by mCCA that showed significantly different loading for schizophrenia patients versus controls, as well as the t-test comparison between three-way and two-way fusion.

callosum connections to temporal lobe (Woodruff et al., 1993; Downhill et al., 2001). While for joint source 4, larger thalamic WM concentrations were shown in schizophrenia, suggesting that GM difference in the parietal and frontal lobe are associated with WM difference in thalamus, consistent with the role of the thalamus as a relay station (Wolfarth et al., 1985). In summary, jICA provides a unified framework to identify joint GM–WM sources that show group differences, which can cover as much neurological ground in a single computational model as achieved by many traditional separate analyses (Shenton et al., 2001).

Moreover, the inter-relationship between GM and WM can be analyzed to identify the tissue distribution abnormalities in schizophrenia (Xu et al., 2011) by utilizing novel features called structural phase and magnitude images. Where the phase image indicates the relative contribution of GM and WM, and the magnitude image reflects the overall tissue concentration. Six networks were identified showing significantly lower WM-to-GM in schizophrenia, including thalamus, right precentral–postcentral, left pre-/post-central, parietal, right cuneus–frontal, and left cuneus–frontal sources. Such findings demonstrate that structural phase and magnitude images can naturally and efficiently summarize the associated relationship between GM and WM.

FUNCTION–STRUCTURE

Cognitive dysfunction present in schizophrenia is often thought to be driven in part by disorganized connections between higher-order cortical fields, thus the combination of function and structure may provide more informative insights into altered brain connectivity (Rykhlevskaia et al., 2008).

Functional magnetic resonance imaging–GM

Figure 3 (Calhoun et al., 2006a) shows analyzed data collected from groups of schizophrenia patients and HCs using the jICA approach. The main finding was that group differences in bilateral parietal and frontal as well as posterior temporal regions in GM distinguished groups. A finding of less patient GM and less hemodynamic activity for target detection in these bilateral anterior temporal lobe regions was consistent with previous work. An unexpected corollary to this finding was that, in the regions showing the largest group differences, GM concentrations were larger in patients versus controls, suggesting that more GM may be related to less functional connectivity during performance of an auditory oddball task. Correa et al. (2008) also showed an interesting joint relationship between fMRI and GM by mCCA, with patients with schizophrenia showing more functional activity in motor areas and less activity in temporal areas associated with less GM as compared to HCs.

Michael et al. (2010) introduced a method to identify inter-correlations among GM and fMRI voxels within the whole brain by reducing the cross-correlation matrix into histograms. Results show that the linkage between GM and functional activation in an auditory sensorimotor task (Schroder et al., 1999) is stronger in HCs than patients with schizophrenia. Specifically, GM regions in the cerebellum show more significant positive correlations with functional regions in HC. The cross-correlation can also be reduced to brain clusters (Michael et al., 2011) by fusing GM and fMRI contrast maps of a working memory task (Manoach et al., 1999). The maximum group difference occurred in medium difficulty working memory load. Particularly, the inter-cluster GM-Probe correlations for this load were positive in controls but negative in schizophrenia. While within one group, the inter-cluster correlation comparisons show no differences in controls but in patients with schizophrenia, indicating that the function-structure integrity during the recognition phrase is aberrant in schizophrenia.

Functional magnetic resonance imaging–DTI

Functional magnetic resonance, as a well-established neuroimaging technology, can act as a reference framework for validating conclusions derived from the relatively newer DTI method (Reinges et al., 2004), which can provide information regarding the integrity of WM tracts. Other recent work has shown that brain anatomical and functional connectivity are both altered in schizophrenia (Skudlarski et al., 2010).

Schlosser et al. (2007) observed a direct correlation in schizophrenia between frontal fractional anisotropy (FA) reduction and fMRI activation in regions in prefrontal and occipital cortices, which highlights a potential relationship between anatomical

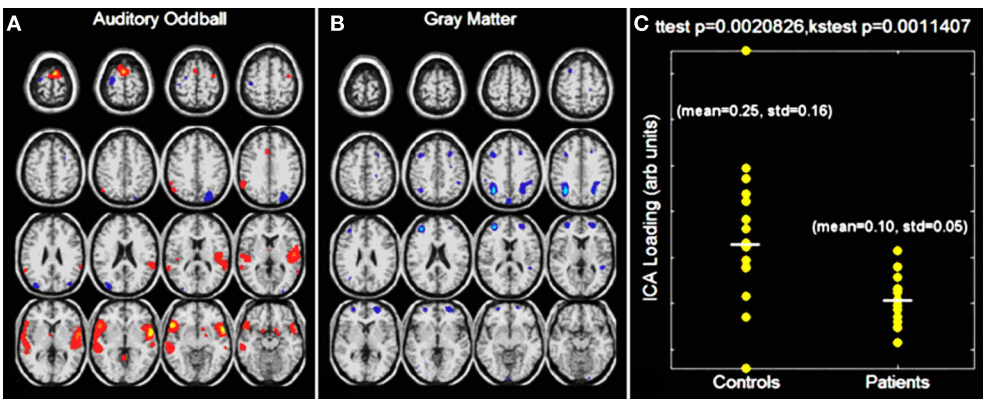


FIGURE 3 | Auditory oddball/gray matter jICA analysis. Only one component demonstrated a significant difference between patients and controls. The joint source map for the auditory oddball fMRI data **(A)** and gray matter **(B)** data is presented along with the loading parameters for patients and controls **(C)**.

changes in a frontal-temporal anatomical circuit and functional alterations in the prefrontal cortex.

Sui et al. (2011) applied a blind data-driven model, mCCA + jICA, optimized for identifying correspondence across modalities, to real fMRI–DTI datasets from 164 subjects, including 62 HC, 54 SZ, and 48 bipolar disorder (BP) subjects. Only one joint group-discriminating component was detected between SZ and HC, including DLPFC and motor regions in fMRI of an auditory oddball detection task as well as parts of the ATR, SLF, and IFO WM tracts. The loading parameters of each modality also showed significant correlations with age. AOD_IC1 represents activations mainly in motor cortex, accompanied by a functional asymmetry with left dominance; see **Figure 4A**, consistent with the fact that the AOD task design required participants to push the button with fingers on their right hand. Controls had a very significant correlation $r = 0.5$, $p = 4e-5$, while patient groups did not (p does not pass correction for multiple comparisons), implying that the motor regions of HC are normally more involved in the task with increasing age (Bennett et al., 2010), whereas schizophrenia patients have no such trend due to presumed motor system deficits (Rogowska et al., 2004).

Fractional anisotropy_IC1, as shown in **Figure 4B**, as a joint component of AOD_IC1, also demonstrated a significant ($p = 2e-08$), but anti-correlation with age. Note that all groups had low p values for this component, thus using one marker, suggesting all subjects have a general age-related decrease in WM integrity, in agreement with (Sullivan and Pfefferbaum, 2003; Grieve et al., 2007). We are also able to provide insights into the high-level brain function-structure network, which verified that the linked (joint) components do correspond to FA changes in known tracts and functional changes in distant regions connected to that tract (**Figure 4C**). Note that we are not directly performing fiber tractography; a strength of mCCA + jICA is that it can detect complicated FA/fMRI relationships without requiring a directly detected link.

BRAIN IMAGING–GENOTYPE

Understanding genetic influences on both healthy and disordered brain function/structure is a major focus of psychiatric neuroimaging ("imaging genomics") and may provide important additional information. For example, using combined genetic and fMRI data can achieve better classification accuracy than using either alone (Yang et al., 2010), indicating that genetic and brain function represent different, but partially complementary aspects.

Functional magnetic resonance imaging–SNP

Liu et al. (2009) first proposed parallel ICA to investigate correlations between brain dysfunctional regions and putative disease susceptibility SNPs, as shown in **Figure 5**. A correlation of 0.38 between one fMRI component and one SNP component was found; both showed significant differences in loading parameters between the schizophrenia and control groups ($p = 0.0006$ for the fMRI; $p = 0.001$ for SNP). The fMRI component consisted of regions in parietal lobe, right temporal lobe, and bilateral frontal lobe. The relevant SNP component was contributed to significantly by 10 SNPs located in genes including those coding for the nicotinic alpha-7 cholinergic receptor (CHRNA7), aromatic amino acid decarboxylase (AADC), and disrupted in schizophrenia 1 (DISC1). The findings provide a proof-of-concept that genomic SNP factors can be investigated by using phenotypic imaging findings in a multivariate format.

Meda et al. (2010) further extended the use of parallel ICA by simultaneously analyzing fMRI and 24 SNP markers that previously had been associated with schizophrenia. Three fMRI components (including PFC, ACC, STG, and MTG) correlated significantly with two distinct gene components including DAT and SLC6A4_PR, revealing specific interactions between schizophrenia risk genes on imaging phenotypes that represent brain function in attention/working memory/goal directed behavior, establishing a useful methodology to probe multivariate genotype–phenotype relationships.

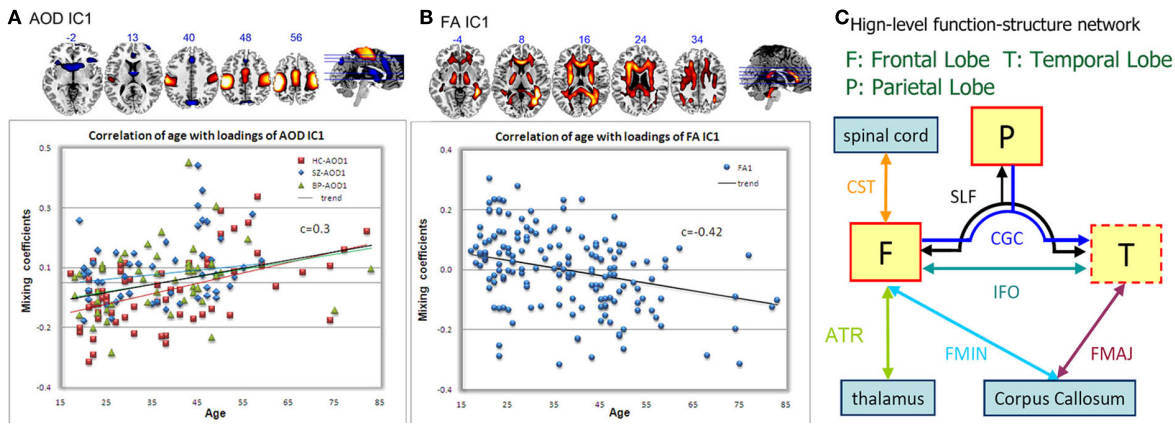


FIGURE 4 | Joint fMRI/FA component that is HC–SZ discriminative, from Sui et al. (2011). Spatial maps of the identified functional blobs **(A)** and WM regions **(B)** are displayed with the correlation plot between subjects' loadings and ages. Specifically, HC in red line, SZ in blue line, BP in green line, and trend of all subjects in black line. **(C)** Shows a high-level brain interaction diaphragm according to the joint component. Functional region with a red solid line frame indicates a major portion activation and the dotted line frame indicates that only small part of it is activated. Abbreviations are defined below, SLF, superior longitudinal fasciculus; CST, corticospinal tract; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; ATR, anterior thalamic radiation; CGC, cingulum; FMAJ, forceps major; FMIN, forceps minor.

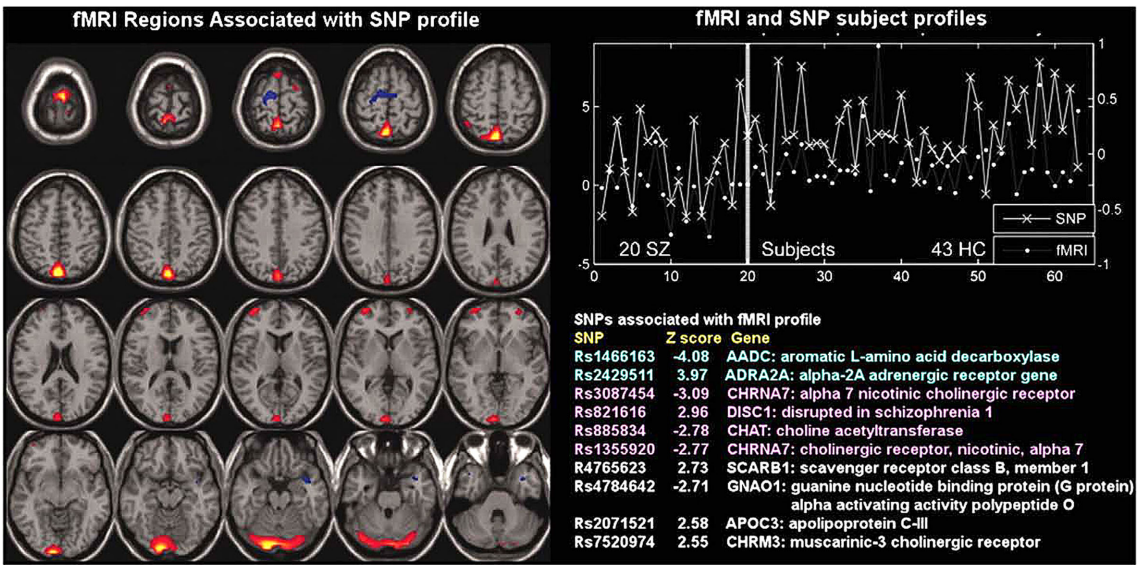


FIGURE 5 | Functional magnetic resonance imaging/SNP parallel ICA from Liu et al. (2009): parallel ICA provides an fMRI part (left) and a SNP part (bottom right) in addition to a correlated subject profile for both fMRI and SNP data (top right).

STRUCTURAL MRI–SNP

Jamadar et al. (2011) further adopted parallel ICA to examine the relationship between GM volumes and 16 SNPs spanning FOXP2 and four Reading Disability-related genes: DCDC2, DYX1C1, KIAA0319, and TTRAP. Five such GM–SNP relationships were identified. The superior prefrontal, temporal, and occipital networks were positively related to DCDC2 in the schizophrenia, but not control group. In addition, the identified networks closely correspond to the known distribution of language processes in the cortex. Thus, reading and language difficulties in schizophrenia may be related to distributed cortical structural abnormalities associated with Reading Disability-related genes.

Similarly, Jagannathan et al. (2010) linked sMRI and genetic (SNP) components using parallel ICA, and identified a sMRI component that significantly correlated with a genetic component ($r = -0.54$, $p < 0.00005$), which also distinguished SZ from HC. The GM deficits pointed to brain regions including frontal/temporal lobes and thalamus ($p < 0.01$), which are consistently implicated in previous reports. These deficits were related to SNPs from 16 genes associated with schizophrenia risk and/or involved in normal central nervous system development, such as AKT, PI3K, SLC6A4, and DRD2.

As to the neurodevelopmental and life span factors in schizophrenia, first episode and longitudinal computed tomography (CT), and MRI studies have shown that brain abnormalities in schizophrenia are present at onset of psychosis and are non-progressive (Nasrallah et al., 1986; Wood et al., 2009). These and other findings support the idea that schizophrenia is a developmental rather than a degenerative condition (e.g., Rund, 2009). Furthermore, the presence of ventriculomegaly and diminished hemispheric asymmetry in familial schizophrenics and in those of their relatives who appear to be transmitting the disorder, implies involvement of the genes controlling neurodevelopment (Frangou and Murray, 1996). All these evidence suggests that genetic vulnerability, environmental factors, and cerebral structural disturbances can act in combination to result in clinically manifest schizophrenia (Harrison and Owen, 2003). Fusion approaches can be used to characterize such changes by relating the fusion parameters with variables such as age (Sui et al., 2011).

SUMMARY OF MULTIVARIATE METHODS

In summary, studies featuring multimodal combinations prove to be more informative in understanding brain activity and disorders and the complexities of schizophrenia make this disease an appropriate test bed for exploration using joint information derived from multimodal datasets. The existing multivariate fusion methods have different optimization priorities and limitations. Each method presents a different view in interpreting and connecting the multiple datasets based on their various hypotheses. In **Table 1**, we listed several multivariate fusion methods that have been applied in schizophrenia study. The following aspects are compared in detail, including feasible combinations, optimization assumptions, purpose of the analysis, requirement of priors, the number of the modalities that can be combined and the input data types, which may serve as a guideline on method selection based on a given research and data.

In addition, for most of the above mentioned models, their inputs are from outputs of the general linear regression model. Since the statistical testing being performed is on the loading parameters within a regression framework, the statistical issues are similar to any regression analysis. Since small sample sizes may not generate enough statistical power, one major means to improve our results is to analyze data from more subjects, perhaps via multisite analyses. For example, in Sui et al. (2011), at least 48 SZ and 37 BP are needed to detect differences from HCs at a power of 0.8. More generally, when the effect size is 0.5, at least 64

Table 1 | Multivariate methods comparison and their applications to schizophrenia.

Methods	Combinations	Studies	Optimization assumptions	Goals and purposes	Need of priors	No. of modality	Input data
Joint ICA	fMRI–sMRI (GM), fMRI–EEG, fMRI–DTI (FA), GM–WM	Calhoun et al. (2006a), Calhoun et al. (2006b), Eichele et al. (2009), Calhoun et al. (2011), Franco et al. (2008), Xu et al. (2009)	$\mathbf{X_1}$ and $\mathbf{X_2}$ share the same mixing matrix, $\mathbf{A_1} = \mathbf{A_2}$. The independence among joint components [$\mathbf{S_1}$, $\mathbf{S_2}$] is maximized	To examine a common mixing modulation across subjects among modalities and to find the linked source maps	No	2 is preferred, 3+ is possible	Features*
Multimodal CCA	fMRI–EEG, fMRI–sMRI (GM)	Correa et al. (2008), Correa et al. (2010b), Correa et al. (2010a)	Maximizes covariation of the mixing profiles across the two datasets, $corr(\mathbf{A_1}, \mathbf{A_2}) = diag(r_1, r_2 \ldots r_m)$	To detect common as well as distinct level of connection between subject modulation	No	2 is classical, 3+ is possible	Features or raw data
mCCA + jICA	fMRI–DTI (FA)	Sui et al. (2011)	Assume the decomposed component from each modality have some degree of correlation between subject-mixing profiles. mCCA is first used in order to make the jICA job more reliable by providing a close initial match via correlation; jICA further separates the remaining mixtures in the joint maps	To achieve both flexible modal association (high or low correlation) and accurate source separation. It is easily to be applied to 3+ modalities	No	2+ is preferred	Features
Parallel ICA	fMRI–gene (SNP), GM–gene (SNP)	Liu et al. (2009), Meda et al. (2010), Jagannathan et al. (2010), Jamadar et al. (2011)	Maximizes the cost function based on both entropy (for all components) and the correlation term (for components whose the mixing profile correlations are above the threshold) by enhancing intrinsic interrelationships of the ICs	To identify both independent components and flexible connections between two modalities. It has been applied widely in fusion of imaging and genetic data	Yes	2	Features
CC-ICA	multitask fMRI (can also be applied to multimodal fusion)	Sui et al. (2009), Kim et al. (2010)	All modalities share a same subject-mixing matrix and a group difference criterion is incorporated into the traditional ICA cost function to be maximized. CC-ICA is optimized for detecting group differences	To improve the sensitivity of the components extraction to group differences as well as the decomposition accuracy	Yes	2 is preferred, 3+ is possible	Features
Other models	fMRI–EEG, fMRI–MEG, MRT–DTI	Eichele et al. (2005), Astolfi et al. (2004), Kubicki et al. (2003), Michael et al. (2011), Michael et al. (2010)					

**Here the "feature" is defined as a distilled dataset representing an interesting part of each modality and it contributes as an input vector for each modality and each subject. The raw high dimensional data is preprocessed to generate a second-level output (that is "feature"), which can be a contrast map calculated from task-related fMRI by the general linear model, a component image from a first-level ICA, an FA map from DTI data, or channels from raw EEG signals.*

subjects are needed per group ($N = 2$) to reach a statistical power of 0.8 in detecting group differences (Kenny, 1987).

Note that there are several other multivariate methods that have been successfully applied to brain imaging data fusion in other mental illnesses, such as Alzheimer's disease, but have not yet been applied to schizophrenia. These methods include but not limited to partial least squares (Chen et al., 2009), linked ICA (Groves et al., 2011), and dynamic Bayesian networks (Plis et al., 2010). Hence, a future direction may lie in utilizing such approaches to explore schizophrenia.

In conclusion, the use of data fusion is a powerful technique. Selecting which fusion model to use should be done carefully but can be somewhat daunting, as there are many approaches available already. We have attempted to characterize and compare some of the available models in this paper. The use of data fusion approaches can help better elucidate the relationship among multiple modalities and facilitate new discoveries in brain disorders. The most promising avenues for future schizophrenia study may rest on developing better models that can complement and exploit the richness of the various data sets (Friston, 2009) and may enable a broader neuroscience perspective to be applied to neuroimaging so that key questions can be addressed in a theoretically grounded fashion.

Finally, certain caveats must also be considered in reviewing the evidence summarized in this paper. Schizophrenia is a clinically defined syndrome currently lacking specific biologic markers (biomarkers), though some robust deficits have been frequently identified in specific modalities, e.g., the DLPFC and superior temporal gyrus regions in MRI (Calhoun et al., 2004; Kim et al., 2009; Xu et al., 2009; Correa et al., 2010b), the ATR in WM tracts (Kubicki et al., 2005a; McIntosh et al., 2008a; Sui et al., 2011), and genetic differences in CACNA1C, DISC1, etc. (Liu et al., 2009; Williams et al., 2009). Thus, it is certainly possible that "schizophrenia" represents an agglomeration of biologically distinct diseases gathered by clinicians into a clinically convenient but biologically unrelated category of convenience, analogous to "dropsy." To that extent this is true, no analyses will likely detect a uniform set of biomarkers to delineate a single disorder, because there are multiple disorders. The second caveat is that the overwhelming majority of schizophrenia subjects studied in the studies summarized are treated with powerful psychotropic medications that potentially alter both brain structure and function, so that commonalities detected in these imaging studies may in part result from such treatments for the disorder rather than being primary; this issue can only be resolved by studying first-episode drug-naïve subjects.

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An ICA with reference approach in identification of genetic variation and associated brain networks

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To address the statistical challenges associated with genome-wide association studies, we present an independent component analysis (ICA) with reference approach to target a specific genetic variation and associated brain networks. First, a small set of single nucleotide polymorphisms (SNPs) are empirically chosen to reflect a feature of interest and these SNPs are used as a reference when applying ICA to a full genomic SNP array. After extracting the genetic component maximally representing the characteristics of the reference, we test its association with brain networks in functional magnetic resonance imaging (fMRI) data. The method was evaluated on both real and simulated datasets. Simulation demonstrates that ICA with reference can extract a specific genetic factor, even when the variance accounted for by such a factor is so small that a regular ICA fails. Our real data application from 48 schizophrenia patients (SZs) and 40 healthy controls (HCs) include 300K SNPs and fMRI images in an auditory oddball task. Using SNPs with allelic frequency difference in two groups as a reference, we extracted a genetic component that maximally differentiates patients from controls ($p < 4 \times 10^{-17}$), and discovered a brain functional network that was significantly associated with this genetic component ($p < 1 \times 10^{-4}$). The regions in the functional network mainly locate in the thalamus, anterior and posterior cingulate gyri. The contributing SNPs in the genetic factor mainly fall into two clusters centered at chromosome 7q21 and chromosome 5q35. The findings from the schizophrenia application are in concordance with previous knowledge about brain regions and gene function. All together, the results suggest that the ICA with reference can be particularly useful to explore the whole genome to find a specific factor of interest and further study its effect on brain.

Keywords: independent component analysis with reference, genome-wide association study, brain network, schizophrenia, single nucleotide polymorphisms, functional magnetic resonance imaging

INTRODUCTION

Considerable research suggests that complex genetic factors contribute to the etiology of mental diseases including Alzheimer's, Parkinson's and schizophrenia (Serretti et al., 2007; Allen et al., 2008; Simon-Sanchez et al., 2009). For instance, schizophrenia is highly heritable, with heritability of 0.6–0.8 (Rao et al., 1981) and the concordance between identical twins is about 50% (Cannon et al., 1998), suggesting roles for both genetic and environmental influences. Linkage studies on family samples and association studies on population samples both identify multiple genetic variants associated with the disease (Hovatta et al., 1998; Levinson et al., 2000; Fan et al., 2006; Purcell et al., 2009). One way to test the genetic risk is to perform a focused study on a selection of specific genes or chromosome loci, which are hypothesized to relate to the disorder-based on *a priori* knowledge of the molecular and cellular functions. While useful, this approach may overlook genetic elements that have not yet been studied but may actually play an important role in a given disorder. This limitation, combined with the known genetic complexity of many diseases, provides strong motivation for performing a broad genome-wide association study (GWAS) on a large number of single nucleotide polymorphisms (SNPs).

GWAS methods enable the study of genes that have not been studied or that have been understudied for a particular disease (Hirschhorn and Daly, 2005) and thus, hold considerable potential for identifying genes associated with complex genetic illnesses (Hindorff et al., 2009). Unfortunately, GWAS is not without its own shortcomings. The main challenge is a statistical power limitation, which is further exacerbated if only a limited number of subjects are available. To balance a small sample size and a large volume of SNP data, a set-based approach has been proposed that, instead of testing the association of each genetic marker one by

one, tests the overall effect of multiple markers grouped by genes (Liu et al., 2010) in hope of a larger effect size and increased statistical power. Similar is a factor-based GWAS approach, where a factor comprises multiple markers carrying a related pattern.

Among many factorization methods, independent component analysis (ICA), multiple regression, and partial least squares have been applied in GWAS. For example, ICA or parallel ICA (Liu et al., 2008) has been implemented to identify genetic factors and associated phenotypic factors (Lee and Batzoglou, 2003; Dawy et al., 2005; Liu et al., 2009). A genetic factor is a weighted combination of multiple loci statistically associated, while different alleles contribute with different effect size to a phenotype. The number of independent factors extracted and analyzed is remarkably smaller than the number of genetic markers, which serves as a high-dimension reduction function. Recently, Vounou and colleagues proposed a sparse reduced-rank multiple regression to discover genetic associations with neuroimaging phenotypes, wherein the reduced-rank regression was employed to tackle the dimension reduction and a sparsity control was used to select highly predictive genetic markers (Vounou et al., 2010). These methods all have shown an ability to extract factors accounting for major variance from genetic data. Yet, in some cases, particularly with up to a million loci, researchers are still facing challenges in extracting factors of specific interest that may not carry a large amount of variance in the genome. In this paper we present a procedure to extract a maximally independent genetic factor of a particular interest by using *ICA with reference*, where ICA is constrained with a user-defined reference. We then are able to investigate the relationship of this particular genetic factor with brain function by using functional networks extracted from functional magnetic resonance imaging (fMRI) as phenotypes.

Using brain function measured by fMRI data has become popular recently as an intermediate phenotype for genetic studies of mental illnesses. For complex genetic mental disorders such as schizophrenia, structural and functional alterations in the brain have been observed consistently including major deficits in dorsolateral prefrontal cortex (Weinberger et al., 1986; Potkin et al., 2009), superior temporal lobe (Calhoun et al., 2008; Sun et al., 2009), etc. Meanwhile, multiple alleles, genes, and their interactions (Prata et al., 2009; Meda et al., 2010) have shown to modulate the risk to schizophrenia (current reports are available at the schizophrenia forum gene list at http://www.schizophreniaforum.org/). All the brain abnormalities together with the genetic complexities make schizophrenia a good target of our proposed reference ICA approach with brain functional phenotypes.

In this study, we test our method on both simulated and real datasets for association between fMRI and SNPs. The real data were obtained through the Functional Biomedical Informatics Research Network (FBIRN), a multi-site study sponsored by the NCCR/NIH which included the development of multi-center fMRI techniques with schizophrenia-related fMRI data collection, and genetic sample collection (Friedman et al., 2008; Potkin and Ford, 2009). The fMRI data were collected from subjects as they performed four sessions of a two-tone auditory oddball task. This task was selected given that previous studies have consistently linked schizophrenia with deficits in both strength and extent of activation during auditory target detection tasks (Kiehl and Liddle, 2001; Li et al., 2002).

METHODS AND SIMULATION

OVERVIEW OF DATA ANALYSIS APPROACH

We propose a multistep approach to identify a specific (e.g., disease-related) genetic variation and the associated brain networks using a guided version of ICA. A flowchart of our approach is shown in **Figure 1**. The starting point is to find reference markers that present prominent feature of interest. The reference markers can be derived from prior knowledge about genes' function or data pattern. Once identified, these markers (called a reference) are used to guide the ICA process to extract an independent component maximally representing reference's characteristics from a much large array. This process is known as ICA with reference. While extracting the independent component, ICA also outputs a set of subject-specific loading coefficients, which describe the presence of the identified component across subjects. We then extract brain functional networks from fMRI images using a regular ICA, where each fMRI component identified presents a brain network. Finally, we correlate the loading coefficients of the resulting fMRI components to the loading coefficients of the SNP component to identify linked SNP/fMRI component pairs and their relationship.

REFERENCE GENERATION

As mentioned above, a reference can be generated in many ways, such as from a particular feature in the genetic data, or from a hypothesized pathway or a cluster of prior loci. For the purposes of this study we assume that the true susceptible loci show prominent differences in allelic frequency between patients and controls, and a majority of them are operating together. Based on this assumption, we identify the SNPs showing group differences using a two-sample t-test $p < 0.0001$ (uncorrected for multiple tests, empirically chosen for conveying the pattern of interest, and, at the same time, not introducing irrelevant data) as the reference. This reference selection is not meant to claim these SNPs are significant at a GWAS level, but to identify a pattern of interest.

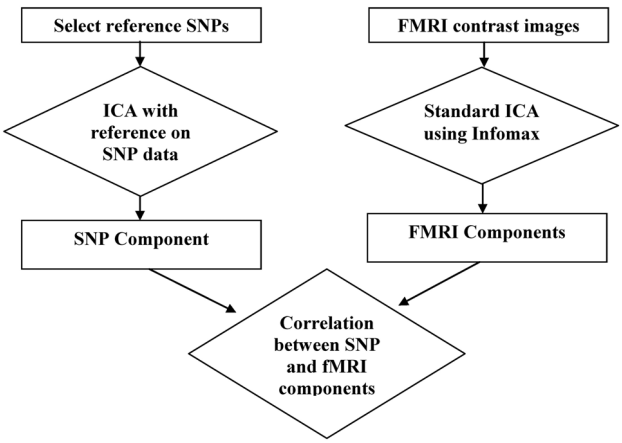

FIGURE 1 | The flowchart of the proposed method.

The location of the reference SNPs provides a set of weights to guide the ICA with reference to find the best SNP factor associated with the disease in the sample.

ICA WITH REFERENCE ON SNPs

ICA is a generic technique that extracts a set of underlying components or factors from a set of random variables or observations. The components themselves are assumed to be mutually independent and linearly mixed into observations. Explicitly, if we consider n component signals $s = [s_1, s_2, \ldots s_n]^T$ and assume they are linearly mixed together to produce m observations, the generative model can be written as $x = As$, where A is the mixing matrix. Elements of A are often referred to as mixing or loading coefficients. ICA attempts either to estimate the mixing matrix A, or find its pseudo-inverse W referred to as the de-mixing matrix; so that the elements of $y = Wx$ are a good representation of s, the component signals. The estimation and optimization of W is based upon the assumption of mutual independence between the component signals.

ICA with reference is based on one ICA algorithm, the FastICA algorithm (Hyvirinen and Oja, 1999; Bingham and Hyvarinen, 2000), where the negative entropy is used to measure mutual independence in a formula as max: $J(y) \sim [E\{G(y)\} - E\{G(\varphi)\}]^2$. φ is a standardized Gaussian variable and $G(\cdot)$ is a non-quadratic contrast function. While optimizing $J(y)$, the Kuhn–Tucker conditions can be used along with the notation $y = w^T x$ and the constraint $||w||^2 = 1$ to yield an update on the rows of W, such that $w_k = E[xG'(w_{k-1}^T x)] - E[G''(w_{k-1}^T x)]w_{k-1}$. If a function $G'(u) = u^3$ is chosen, the update becomes $w_k = E[x(w_{k-1}^T x)^2] - 3w_{k-1}$. Inspired by this form of the update, it is possible to impose an additional constraint which incorporates prior information about the components (Barros and Cichocki, 1998; Lin et al., 2007). Such a method has previously been applied to fMRI data (Lin et al., 2010) and is implemented within the GIFT toolbox (http://icatb.sourceforge.net). If the components are also known to be sparse, i.e., only have activity of interest in a small section of all variables, which is true for most genetic factors in the genome, then that information can also be incorporated into the previous update on w by considering $w_k = E[x|w_{k-1}^T x - r|^p \text{sign}(w_k^T x - r)] - 3w_{k-1}$, where r is a reference signal containing source activity information, and $|\cdot|^p$ is a p-norm based closeness measure. This update is no longer maximizing just the independence, but finding the maximally independent source which is close in the $|\cdot|^p$ sense to the reference. Strictly speaking the update no longer produces maximally independent sources; however, it is often reasonable to relax the independence assumption when there is sufficient prior information about the component structure (Barros and Cichocki, 2001).

Using the reference identified in Section "Reference Generation," we apply the ICA with reference to the large SNP data to determine the component with the closest distance to the reference. In detail, the input to the ICA with reference includes an M-by-P SNP matrix, where M is the number of samples and P is the number of SNP loci in a range of 10,000–300,000 in this study. The SNP data are coded as 0, 1, or 2, indicating the load of minor alleles. A reference is also provided that is a 1-by-P vector consisting of 0 s and 1 s with 1 denoting reference loci. The identified SNP component by the ICA with reference represents a maximally independent genetic factor comprising multiple SNPs, of which each has its specific contribution, and may come from different genes or even different chromosomes, but carries covaried distribution across subjects to be classified into one genetic factor. Since this factor is derived using a reference with different allelic frequency between groups, we expect it to differentiate patients from controls, which can be verified through a two-sample t-test. Here the purpose of the t-test is not for significance of group difference (which is biased due to the reference), but for verification of the property of the desired component. For interpretation of our results, we normalize the contribution weights of the component (using z-transform) and select only the top 0.05% SNPs in the contribution distribution (including positive and negative). This conservative cut-off (similar to $\alpha = 0.0005$) provides us with a subset of SNPs which contribute the most to the component. To further analyzing the inter-relation among the top SNPs, we perform cross-correlation tests on the genotypes of these SNPs across subjects and linkage disequilibrium (LD) test. The D′ (normalized LD) values between pairs of SNPs were calculated by the PLINK tool (http://pngu.mgh.harvard.edu/∼purcell/plink/).

ICA ON fMRI

Since brain function is the phenotype of this study, we extracted independent brain networks from fMRI images using a regular (blind) ICA, the infomax algorithm (Bell and Sejnowski, 1995). Infomax requires estimating the number of independent components first. To determine this number, we performed both the modified minimum descriptive length algorithm (Li et al., 2007) and the Akaike information criteria test (Akaike, 1974) and used the rounded average of their results. After fMRI component extraction, we correlated the subject-specific loading coefficients of the fMRI components with those from the SNP component. With 0.05 Bonferroni multiple comparison correction, we identified the significantly correlated SNP-fMRI components, which suggest that the genetic factor has influence on brain function of the identified brain network.

PERMUTATION TEST

To validate our findings on the association between the genetic factor and fMRI networks, we conducted a 10,000-permutation test, by permuting schizophrenia patient (SZ) or healthy control labels of the SNP data and repeating steps 2.2–2.4. Thus, we generated randomly references for the SNP data in each permutation, and extracted a SNP factor and tested its correlation with the fMRI components accordingly. With the 10,000 permutations, we are able to build a distribution of null hypothesis about the correction between the genetic factor and brain networks and examine the significance of the true correction.

SIMULATION TEST ON THE ICA WITH REFERENCE

A simulation was designed to validate the capability of ICA with reference to extract factors of interest, in particular for genomic SNP data. We used the simulation tool in PLINK (http://pngu.mgh.harvard.edu/∼purcell/plink/) to generate a set of 200

subjects and 10,000 SNPs of genotype data with minor allele frequencies (MAF) ranging from 0.01 to 0.5. Although the ICA with reference method is designed to extract any factor of interest, such as a factor of a particular pathway, we simulated a simple case in terms of easy evaluation, which is to extract factors discriminating patients from control groups. We selected six sets of SNPs, each with 10–100 loci, as causal loci for six types of diseases, respectively (these causal SNP loci are not in LD with max correlation < 0.25), and superimposed correlations into these causal loci and diagnostic phenotypes (six sets of diagnoses, each with half patients and half healthy controls). The superimposed correlation between individual causal locus and diagnosis ranged from 0.20 to 0.50, resulting in effect sizes of 0.04–0.25 (percentage of variance explained). It can be seen that some causal loci have very low effect size, even lower than averaged random loci of 0.08. The reference is the location of a handful of SNPs that comprise different proportions of simulated true causal loci and false causal loci. We compared the performance of the reference ICA with that from a regular Infomax ICA. We tested whether the right factor is extracted and the factor's effect size under different configurations of the reference accuracy (the fraction of true causal loci in the reference), and reference length (the number of reference loci relative to the number of all causal loci in the simulation data). Because the targeted factors are the ones discriminating patients from controls, we can further evaluate the sensitivity, specificity, and area under ROC curve (AUC), after thresholding the contribution weight of factors to pick the top contributing loci. To increase the validity of all tests, results presented here were obtained after averaging the six diseases conditions.

APPLICATION IN SCHIZOPHRENIA

SUBJECTS

Subjects used in the real data application were part of FBIRN Phase II study (Kim et al., 2009; Potkin et al., 2009), recruited from seven universities (Duke/University of North Carolina, University of Iowa, Massachusetts General Hospital, University of California–Irvine, University of California–Los Angeles, University of Minnesota and University of New Mexico). All participants provide written informed consent approved by local institutional review board. SZ group met criteria for schizophrenia or schizoaffective disorder-based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Healthy controls (HC) were free of a personal or family (first-degree relatives) history of major axis I psychiatric illness. See the detail in (Kim et al., 2009; Potkin et al., 2009). Out of 186 available subjects, 90 subjects had both genetic and fMRI data from an auditory oddball task. Two subjects were further removed because of problematic fMRI data (motion rotation $> 1.4°$, translation > 4.5 mm). Thus, 40 HC subjects and 48 SZ patients were analyzed in the following application. The patients and controls were similar in handedness, age, race, and parental education level, but the patients had significantly lower IQs and fewer years of education than the HC subjects. See **Table 1** for a comprehensive presentation of subject demographic data.

fMRI TASK AND CONFIGURATION

fMRI images were collected during an auditory oddball task, which consisted of a series of frequent standard (1000 Hz, 95%) or target (1200 Hz, 5%) 100 ms duration tones presented every 500 ms. Subjects were instructed to press a button with their right hand as quickly as possible whenever a target tone was presented. See Kim et al. (2009) for more detailed information about the design of the experiment and the data collection procedures.

Based on performance during preliminary studies, the FBIRN consortium matched their pulse sequence parameters to the greatest extent possible across all sites. The parameters were as follows: slice thickness $= 4$ mm, field of view $= 22$ cm, flip angle $= 90°$, voxel dimensions $= 3.43 \times 3.43 \times 4$ mm, number of slices $= 27$, matrix $= 64 \times 64$, repetition time $= 2$ s, and echo time $= 30$ ms (3T)/40 ms (1.5T). The fMRI data were analyzed using statistical parametric mapping software version 5 (SPM5) (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). fMRI images were motion corrected using INRIalign image realignment, slice-timing corrected, spatially normalized to Montreal Neurological Imaging (MNI) space and then spatially smoothed using a $9 \times 9 \times 9$ mm full width at half maximum Gaussian kernel. The general linear model was applied to get the response maps for the target tone and standard tone, and the target tone minus standard tone contrast image was extracted for each subject. An additional mask was applied to remove voxels from CSF and

Table 1 | Subject demographic information and IQ measurements.

Demographics	Schizophrenia [Mean (SD)]	Healthy controls [Mean (SD)]	*t*/*p* Value
Sex (male/female)	29/19	20/20	–
Race (Caucasian/African American/Asian/Mixed)	38/8/2/0	34/2/2/2	–
Handedness (R/L)	44/4	38/2	–
Age (in years)	38.06 (10.98)	35.29 (10.99)	1.185/0.23
Maternal education (in years)	13.26 (2.99)	14.44 (2.41)	−1.95/0.054
Paternal education	14.07 (3.47)	14.89 (3.29)	−1.08/0.28
Subject education	13.70 (1.912)	15.67 (1.81)	−4.8/7.18E-6
Verbal IQ	103.98 (10.21)	110.79 (6.88)	3.54/7.16E-4
Performance IQ	107.88 (5.07)	110.95 (3.25)	3.27/1.7E-3
Full scale IQ	102.13 (8.96)	112.1 (6.03)	3.54/7.16E-4

Note: IQ data was missing seven subjects from the SZ group.

regions outside the brain. These contrast images were then used to identify independent brain networks as intermediate phenotypes.

GENOTYPING AND PREPROCESSING

DNA samples from 186 subjects were genotyped at 308,330 SNP loci in autosomes using Illumina HumanHap300 BeadChip arrays. The SNP arrays were preprocessed using PLINK V1.07 (http://pngu.mgh.harvard.edu/purcell/plink/). A total of six subjects and 6,509 SNP loci were removed because fewer than 90% of their markers were genotyped correctly. No subject failed the heterozygosity outlier test or the test for second-degree and closer relatedness. The Hardy–Weinberg Equilibrium test in controls eliminated 11 SNP loci with a cut-off $p < 10^{-6}$. Missing genotypes were replaced with the genotypes of the SNPs in the highest LD > 0.8, if available. Otherwise the SNP loci (28,809 SNP loci) were removed. A minor allele frequency of 0.01 was used and resulted in 272,808 SNP loci. These SNPs were coded as 0, 1, 2, indicating the number of minor alleles based on an additive model. Though a three dimensional orthogonal coding (Hardoon et al., 2009) can handle all three models: additive model, dominant, and recessive model, the number of data variables will be increased by a factor of three. In this study we choose the additive model as the most general, and do not want to increase the already large number of data variables. An eigenvalue based approach (Price et al., 2006) was applied to remove population structure effect. Two population stratification components were removed due to significant correlation with race information. Afterward, a Quantile-Quantile plot shows no clear population stratification indication with $\lambda = 1.005$.

RESULTS

SIMULATION RESULTS

Simulated data are 10,000 SNPs' genotypes coded as 0, 1, and 2 from 200 subjects. Six types of disease conditions were built in with each involving 10–100 causal loci and affecting half of subjects. The targeted factors in this simulation are those related to each disease. Our simulation results show that, in most cases (five out of six disease conditions in some simulation runs, and six out of six in others), regular ICA is unable to extract the superimposed disease-related genetic factors due to the small variance accounted for by such factors. Instead, it extracts other factors embedded in the genomic data with large within-sample variances. In contrast, the ICA with reference can extract the right factors under most conditions except when the reference accuracy is really low. With a reference with low accuracy, as indicated by asterisks in **Table 2**, the ICA with reference functions like the regular ICA and produces the same outputs as the regular ICA.

When we have the right factors extracted, we calculated the sensitivity, specificity, and AUC to provide more information about the accuracy of the factors. The sensitivity and specificity to identify causal loci are functions of the Z-score threshold that measures the contribution of each locus to the genetic factor, compared with the ground truth about causal loci. Since the regular ICA cannot extract the right factors in general, the sensitivity and specificity were low and not presented, but similar as the results from the reference ICA under special configurations. In the ICA with reference results, we presented in **Table 2** the sensitivity and specificity for the z-score of 2.5 as a typical example, the AUC and the total factor effect size along with different reference configurations. The results in **Table 2** are the averaged results from six disease conditions. When the reference accuracy is above 0.5, or the reference accuracy is 0.5 and the reference length is above 0.2, the right components were extracted with increased sensitivity of detecting the true causal loci compared with known true causal loci in the reference. But, as shown in **Table 2**, when the reference accuracy is only 0.25 or the reference length is 10–20% with 50% true causal loci, the reference ICA fails to extract the disease-related factors, functions just like the regular ICA, and extracts

Table 2 | Simulation results using 200 subjects and 10,000 SNPs.

Reference length	Reference accuracy	AUC	Sensitivity (Z = 2.5)	Specificity (Z = 2.5)	Discovered total factor effect size
0.1	1	0.94	0.30	0.99	0.28
0.2	1	0.97	0.53	0.99	0.47
0.4	1	0.99	0.71	0.99	0.62
0.5	1	0.99	0.73	0.99	0.64
0.1	0.75	0.93	0.24	0.99	0.25
0.2	0.75	0.91	0.37	0.99	0.31
0.4	0.75	0.98	0.63	0.99	0.52
0.5	0.75	0.98	0.63	0.99	0.51
0.1	0.5	0.82*	0.13*	0.99*	0.11*
0.2	0.5	0.85*	0.23*	0.99*	0.17*
0.4	0.5	0.93	0.44	0.99	0.32
0.5	0.5	0.94	0.45	0.99	0.33
0.1	0.25	0.69*	0.06*	0.98*	0.04*
0.2	0.25	0.72*	0.07*	0.98*	0.04*
0.4	0.25	0.80*	0.12*	0.98*	0.09*
0.5	0.25	0.82*	0.16*	0.98*	0.09*

*Note: *Indicates that a non-disease-related factor was extracted with an effect size same as a random locus.*

factors with the effect size and sensitivity in the range of random loci. Results measured by AUC, sensitivity, and factor effect size are in agreement with each other. We also conducted a simulation with 90 subjects and 230,000 SNPs, a similar scenario to the real data application. The results are very similar to **Table 2** (not shown). Therefore, we assume that in the real data application at least 25% of the reference markers are true causal loci (or tagging loci) for phenotypes of interest.

RESULTS FROM THE APPLICATION IN SCHIZOPHRENIA

In the real application of 88 subjects' SNP genotypes from 272,808 loci, only 25 SNP loci showed a difference between the HC and SZ groups at an uncorrected p-value less than 1×10^{-4}. The location of these 25 SNPs (rs7570354, rs11711733, rs152442, rs10953026, rs2279834, rs1039898, rs10511304, rs2173096, rs511411, rs382321, rs3731920, rs955411, rs4105175, rs17826681, rs1017528, rs1391927, rs7341022, rs1468708, rs9314788, rs1124941, rs2172557, rs6596651, rs2286696, rs1284108, rs1419005) was used as the reference for our ICA with reference analysis on the entire SNP dataset (88-by-272,808 matrix). The extracted SNP component, as we expected, differentiates SZ patients from controls with much lower loadings in patients (p-value of 4.10×10^{-17}. This p value is not meant for unbiased significance, but for verification of the desired property of the genetic factor. The significance of this factor's association with brain function is the targeted test). This SNP component was not confounded by gender and handedness, tested by ANOVA. After normalizing the contribution weights in the identified SNP component using a z-transform, we selected the top 26 SNPs that contribute most, which lie in the top 0.05% of all SNPs contribution distribution in the component (SNPs with a $|Z|$-score greater than 4.68; the contribution weight can be positive or negative). These SNPs, their corresponding genes, chromosome position, and MAF in patients and controls are shown in **Table 3**. All these loci exhibit different MAF between patients and controls (p value ranging from $2.74 \times 10^{-6} \sim 0.04$), with some minor alleles more frequent in patients and some in controls.

To investigate the possible inter-SNP-relationship, we performed cross-correlation tests on the genotypes of 26 contributing SNPs across subjects. **Figure 2** presents all correlations stronger than 0.35 ($P < 0.001$), which forms two big clusters. One is centered at chromosome 7q21 region including rs10953026, rs2286696, rs758706, rs3824039, rs2188240, rs1110457, rs7669821, rs2381387, and rs1419005, mainly involving gene *CDK14*, *NXT1,* and *UGDH*. The other cluster is centered

Table 3 | Top component SNPs by weights and associated genes.

SNP	Contribution weights	MAF: patient	MAF: controls	Chromosome position	Gene
rs10953026*	7.11	0.22	0.54	7q21.13	CDK14[1]
rs2286696*	6.7	0.29	0.61	7q21.13	CDK14[1]
rs4105175*	6.6	0.29	0.55	5q35.3	ZNF879[2]
rs2173096*	6.39	0.28	0.55	5q35.3	Between genes GRM6 and ZNF879[2]
rs758706	−6.12	0.56	0.31	7q21.13	CDK14[1]
rs2067011	−5.79	0.58	0.30	5q35.3	GRM6[2]
rs1889574	−5.65	0.46	0.26	13q12.11	LOC 100506971[2]
rs7669821	5.53	0.36	0.54	4p14	UGDH[1]
rs2279834*	5.31	0.10	0.39	12q23.1	SLC5A8
rs1406002	−5.11	0.48	0.33	2p15	Intergenic
rs1468708*	5.10	0.21	0.51	6q24.1	Intergenic
rs1284108*	4.99	0.24	0.51	11q21	Near MED17 (<20 kbp)
rs1017528*	4.89	0.21	0.41	17q22	Near CUEDC (< 30 kbp)
rs1445846	4.88	0.23	0.44	5q35.3	ZNF354C[2]
rs1445845	4.88	0.23	0.44	5q35.3	ZNF354C[2]
rs1445844	4.88	0.23	0.44	5q35.3	ZNF354C[2]
rs11750568	4.88	0.23	0.44	5q35.3	ADAMTS2[2]
rs1419005*	4.88	0.23	0.51	20p11.21	NXT1 (<1 kbp)[1]
rs887780	4.87	0.24	0.41	6q24.1	Intergenic
rs3824039	−4.86	0.54	0.33	7q21.13	CDK14[1]
rs2188240	−4.85	0.54	0.33	7q21.13	CDK14[1]
rs1110457	−4.85	0.54	0.33	7q21.13	CDK14[1]
rs2839081	4.80	0.36	0.56	21q22.3	Near COL6A1 (<20 kbp)[2]
rs6991271	−4.80	0.59	0.34	8p12	KIF13B
rs2381387	4.70	0.30	0.51	4p14	Near UGDH[1] (<3 kbp)
rs1487074	−4.68	0.40	0.23	2p15	Near EHBP1 (<10 kbp)

*Table is sorted by SNP weights. *Indicates the SNP overlapping with the reference SNPs. MAF (minor allele frequency) was calculated based on our dataset. Two clusters are indicated by superscript [1] and [2].*

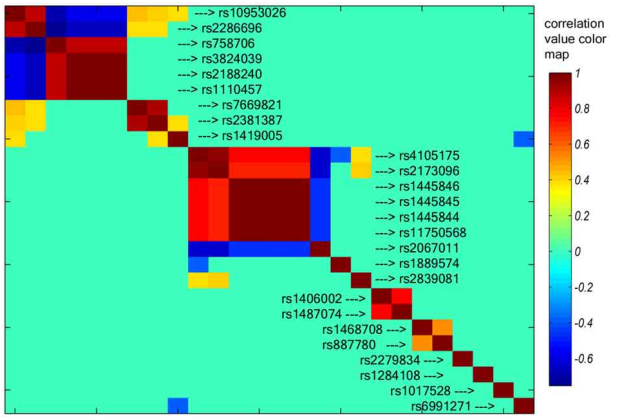

FIGURE 2 | Cross-correlation among the top 26 SNP loci. All correlations stronger than 0.35 were plotted ($p < 0.001$). Two big clusters were identified; one is centered at chromosome 7q21, including rs10953026 and rs2188240. The other is centered at chromosome 5q35 including rs4105175 and rs1445846. See text for the detail list of SNPs.

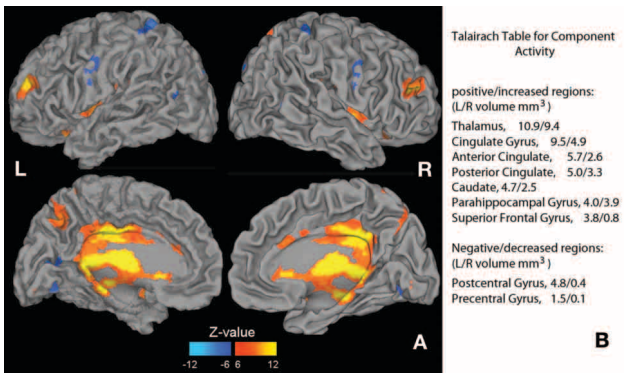

FIGURE 3 | The fMRI component linked to the SNP component. **(A)** Activation map with $|z|$ value > 6 while responding to target vs. standard stimuli in the auditory oddball task. Red to yellow color indicates positive activation regions, while blue indicates deactivation regions. **(B)** A list of regions and volumes with $|z|$ value > 6. The activation regions mainly include thalamus, anterior cingulate and posterior cingulate gyri and deactivation regions are mainly in left pre- and post-central gyri. Note that the pre- and post-central gyri are mainly positively activated during the task, and the deactivation in this component is only fraction of activation that covaries with positive activation in thalamus, cingulate gyrus, etc.

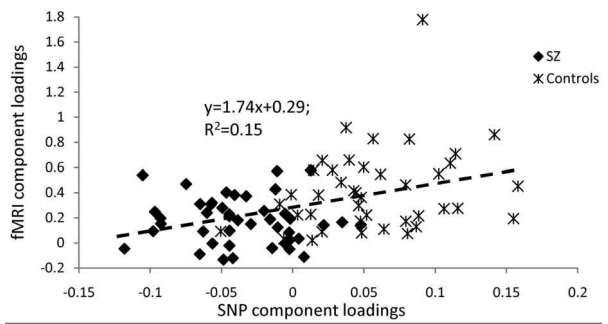

FIGURE 4 | The loading coefficients of the linked SNP and fMRI components. The X and Y axis are the loadings for SNP and fMRI components, respectively. The positive trend shows the positive correlation ($r = 0.39$, $R^2 = 0.15$) between these linked components. Healthy controls demonstrates strong positive presence of the SNP component and higher activation in the fMRI component, while schizophrenia patients carry negative presence of the SNP component (opposite combination of minor alleles in the SNPs), and lower activation in the fMRI component.

at chromosome 5q35 region including rs4105175, rs2173096, rs2067011, rs1445846, rs1445845, rs1445844, and rs11750568, mainly involving gene *GRM6* and *ZNF354C*. No linear correlation exists between these two clusters. The LD tests among the identified 26 SNPs using 180 subjects' data show consistent pattern with the correlation map. The 6 SNPs at 7q21 region are in high LD with D′ of 0.76 ∼ 1, and the 7 SNPs at 5q35 region are also in LD with D′ of 0.74 ∼ 1. The two SNPs at 2p15 are in LD with D′ as 0.93, so are the two SNPs at 4p14 with D′ as 1.

Infomax ICA was performed on the fMRI contrast images to extract functional brain networks. Based upon the dimensionality estimation, we identified five spatially independent fMRI components. Of the five fMRI components, a single component was identified to be significantly correlated with the SNP component (shown in **Figure 3**), with a correlation of 0.39 ($p < 0.0001$, passing Bonferroni correction for multiple comparisons). The loading coefficients of the linked fMRI and SNP components are plotted in **Figure 4**, where the positive correlation indicates that activity in the network shown in **Figure 3** increased as the presence of SNP component increased, with 15% of brain activity variance explained by the SNP component. The *post-hoc* ANOVA tests did not detect any main effect from gender, data collection site, or handedness for this fMRI component. Yet, this fMRI component shows a significant difference between the SZ and HC groups ($p < 0.0001$) on the loading coefficients, which is in accordance with the hypothesis that the genetic risk factor to SZ alters the brain function that also differentiates patients. Permutation results show that the correlation of 0.39 between the genetic factor and brain network has a 0.02 false positive rate among 10,000 random runs.

DISCUSSION

ICA with reference is designed for the extraction of component corresponding to a particular interest. Our goal in this study is not to develop a better classification/discrimination method such as linear discriminant analysis, yet to extract factors of any interest, in particular when the variance carried by such factors is small. In the simulation we only compared the ICA with reference method with a regular ICA method to improve or extend the ICA application to large genetic data.

The simulation results demonstrate that the reference does help to extract the factor of interest, even when the variance accounted for by the factor is very small and regular ICA failed to identify it. It is necessary to point out that the accuracy of the reference is far more critical to the success of the method than the number of loci in the reference. **Table 2** shows that AUC is highest when the reference accuracy is maximized. With the same accuracy, the length of the reference also has an impact on sensitivity

and factor effect size. Not surprisingly, the simulation shows that when the reference is irrelevant to the disease, i.e., many false loci are added, reference ICA extracts a factor either totally unrelated to the disease (In **Table 2** * notes sensitivity and factor effect size close to that from a random individual locus), or with reduced sensitivity and factor effect size. For instance, using only 10% of fully accurate loci produced a higher sensitivity/factor effect size than using 50% of loci of which only half are accurate, equaling to 25% accurate loci. The factor effect size measures the overall effect from multiple small-effect causal loci, calculated by the loadings of the factor and expected to be higher than that from each individual causal locus. The simulation clearly shows that when the right component is extracted, the factor's effect size (> 0.25) is much higher than individual causal locus (0.04–0.25). We are aware that the identification of false positive loci implies that there is certainly room for improvement of the method. Most importantly, the simulation results indicate that even for an imperfect reference (allowing for a maximum of 75% of the reference markers to be incorrect), our method can extract the factor of interest with increased sensitivity, compared to both regular ICA results and known true reference.

For our real data application to a schizophrenia study, we used SNPs that show group differences as the reference for ICA with reference on the entire genetic data set. Even though we are uncertain that all the reference SNPs are the true SZ susceptibility SNPs (or their tagging SNPs), we assume that the true susceptibility loci show prominent differences between patients and controls, and a majority of them are operating together. In the simulation, we proved that as long as 25% of reference loci are true loci or in LD with true loci, then our method can extract the genetic factor with increased sensitivity. Although in the real application we do not know whether 25% of reference SNPs are true SZ susceptibility loci or in LD with true loci (given only 88 samples are used, the fact of 25% of reference SNPs being true SZ susceptible becomes more questionable), this limitation does not affect the method ability to extract a genetic factor differentiating SZ patients from controls in our sample. As a result, 26 SNPs were identified contributing to a genetic component/factor showing significant differentiating power on SZ. Among them, 9 loci overlapped with those from the reference, reflecting the guidance by the reference. The dissimilarities between the identified SNPs in the component and the reference reflect the presence of other SNPs that co-vary with the identified SNPs, but do not show the most significant group difference. Two big clusters found in the 26 SNPs imply that the SNPs may be from different chromosome locations, two major related genetic functions are involved, and the involved SNPs/genes interact together in contributing to the factor that differentiates patients from controls. Essentially, our method serves as a targeted way to extract information embedded in the genome. This approach has many potential applications such as the extraction of a certain pathway-related component from the whole genome.

To study brain functional networks via ICA is a well-established approach (Calhoun et al., 2001; Calhoun and Adali, 2006). Of the five fMRI components extracted in this application, one was significantly correlated with the genetic component, not confounded by gender, collection sites, and handedness (the medication may affect the brain function since all patients except one are under stable doses of psychotropic medication, which is the limitation of this application). The permutation test confirmed this association is within a 0.02 false positive control. The positive correlation between the SNP and fMRI components suggests that the overall effect of this genetic factor is related to a higher activation in regions of this fMRI component. Since each SNP in the genetic factor contributes differently to the factor, some minor alleles such as one in rs10953026 positively relate to increased activation of the fMRI component, and some minor alleles such as one in rs2067011 relate to decreased activation of the brain network. These differences of SNP contribution also reflect their allelic frequency in SZ patients and controls, i.e., MAF of some SNPs is higher in patients, and of others is higher in controls. The identified functional component was mostly notably contained in the cingulate gyrus (anterior cingulate and posterior cingulate) and the thalamus, where SZ patients showed a lower level of activity while responding to target sounds than HCs. The cingulate gyrus, particularly anterior cingulate, is also one of the most studied regions for SZ, where functional and anatomical alterations have been reported in numerous strands of investigations, reviewed by Adams and David (2007) and Fornito et al. (2009), respectively. The thalamus plays a key role in information relay; a defect in connecting the thalamus with frontal cortex and cerebellum could easily explain a wide range of schizophrenia related symptoms. As neuropathology and imaging studies suggested, patients with schizophrenia may have abnormalities in this circuitry (Andreasen, 1997; Shenton et al., 2001; Watis et al., 2008). Our result linking the genetic factor that differentiates SZ patients from controls to the functional differences in these regions is in accordance with the previous knowledge and further increases our confidence on the method.

We were also encouraged by the fact that some of the genes listed in **Table 3** have a direct link to brain function. As presented in the results, these genes are centered at two big clusters, around *CDK14* (7q21) and *GRM6* (5q35). *CDK14* encodes the cdc2-related protein kinase, *PFTAIRE*, that is expressed in postmitotic neuronal cells both in the brain and the embryo (Lazzaro et al., 1997). While not itself a risk gene for schizophrenia, it plays a role in the Wnt signaling pathway (Davidson and Niehrs, 2010), which has been implicated in the pathogenesis of schizophrenia [for review, see (Freyberg et al., 2010). *GRM6* (metabotropic glutamate receptor 6), though expressed in brain (Allan brain atlas gene expression), has not been studied for the mental illness yet and is predominantly associated with visual deficits (O'Connor et al., 2006). Furthermore, it is a member of the mGlu group III receptors, of which *GRM7* and *GRM8* have been implicated in schizophrenia in Japanese populations, e.g., (Takaki et al., 2004; Shibata et al., 2009)], and subgroups of the mGlu receptors are promising therapeutic targets for schizophrenia (Wieronska and Pilc, 2009). The simultaneous implication of mGlu receptors and the activations within a network containing the thalamus is intriguing, given the glutamate receptor alterations in the thalamus in schizophrenia (Cronenwett and Csernansky, 2010), but these results must be considered highly preliminary and we only see it as an encouraging fact to promote the method.

Overall, this study is primarily a method study with a preliminary application to GWAS. Based on our results on simulation and real data application, we believe that the ICA with reference approach enables a flexible but focused way to identify the genetic factor of interest. Compared to a full, blind source separation analysis of all SNP data, it is more robust in terms of extracting the "right" component. When the ICA with reference on SNP data is analyzed in conjunction with brain images as an intermediate phenotype, it provides an effective way to analyze the relation between genetic factors and brain networks. In this study, we used markers with certain levels of allelic frequency difference as a reference; it makes the extracted genetic factor biased toward patients vs. controls difference and thus inflates the significance of the *t*-test on SZ vs. HC difference, but it does not affect the association test on brain functional network. In fact, we have used SNPs in gene *DRD2* as a reference and extracted a genetic factor centered at *DRD2* function (results not shown). Yet, this genetic factor did not relate to any brain function in our image data collected in the auditory oddball task, which provides evidence that the association of a specific genetic factor with brain function is not biased. With such a small sample size, we are aware that the result on real data is limited by identification power. Nevertheless, the simulation and real data application show consistently the capability of ICA with reference to extract genetic factors of interest. In conclusion, we propose an approach that provides a particularly useful way to investigate regions of brain activity associated with specific genetic variation. It can be applied to the identification of certain (gene-specific, pathway-specific, etc.) genetic factors from a large genomic array, and the study of specific genetic effect on brain function. We also provide an example of such application that demonstrates the ability to extract genetic factors, analyze inter-SNP relation, identify associated brain network and suggest the genetic (minor allelic) effect on brain. We hope to see the adoption of our method in the future GWAS researches.

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Functional connectivity studies of patients with auditory verbal hallucinations

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Functional connectivity (FC) studies of brain mechanisms leading to auditory verbal hallucinations (AVHs) utilizing functional magnetic resonance imaging (fMRI) data are reviewed. Initial FC studies utilized fMRI data collected during performance of various tasks, which suggested frontotemporal disconnection and/or source-monitoring disturbances. Later FC studies have utilized resting (no-task) fMRI data. These studies have produced a mixed picture of disconnection and hyperconnectivity involving different pathways associated with AVHs. Results of our most recent FC study of AVHs are reviewed in detail. This study suggests that the core mechanism producing AVHs involves not a single pathway, but a more complex functional loop. Components of this loop include Wernicke's area and its right homologue, the left inferior frontal cortex, and the putamen. It is noteworthy that the putamen appears to play a critical role in the generation of spontaneous language, and in determining whether auditory stimuli are registered consciously as percepts. Excessive functional coordination linking this region with the Wernicke's seed region in patients with schizophrenia could, therefore, generate an overabundance of potentially conscious language representations. In our model, intact FC in the other two legs of corticostriatal loop (Wernicke's with left IFG, and left IFG with putamen) appeared to allow hyperconnectivity linking the putamen and Wernicke's area (common to schizophrenia overall) to be expressed as conscious hallucinations of speech. Recommendations for future studies are discussed, including inclusion of multiple methodologies applied to the same subjects in order to compare and contrast different mechanistic hypotheses, utilizing EEG to better parse time-course of neural synchronization leading to AVHs, and ascertaining experiential subtypes of AVHs that may reflect distinct mechanisms.

Keywords: auditory verbal hallucinations, schizophrenia, functional connectivity, functional magnetic resonance imaging, Wernicke's area, putamen, speech

Between 60% and 80% of patients with schizophrenia experience auditory verbal hallucinations (AVHs) of spoken speech (Sartorius et al., 1974; Andreasen and Flaum, 1991). These hallucinations often produce high levels of distress and functional disability and are resistant to conventional treatments. Understanding the mechanism of AVHs may shed light on the pathophysiology of schizophrenia overall, and lead to more specific treatments. Mechanistic models under consideration include abnormalities involving source attribution of ordinary inner speech, abnormalities involving registration and retrieval of acoustic memories, and bottom-up activation of speech processing neurocircuitry (for review see Jones, 2010).

Besides studies of activation associated with AVH occurrences, functional magnetic resonance imaging (fMRI) offers another tool for probing the mechanism of AVHs, namely functional connectivity (FC). FC refers to computational measures derived from inter-region correlations of blood-oxygen-level dependent (BOLD) activity time-course. In theory, FC reflects either direct cross-region interactions or correlated activity arising from inputs from a third, shared source. Computational strategies have been developed that minimize effects of non-neural factors such as vascular physiology and respiration, using, for example, low-pass filtering signals (generally employing a 0.1 Hz cut-off) and removing variance corresponding to slice or whole brain mean time-course. Resting or "no-task" FC has been able to identify functional pathways critical to normal vision, motor function, audition, language, reading, and attention (Biswal et al., 1995; Lowe et al., 1998; Xiong et al., 1999; Cordes et al., 2000; Hampson et al., 2002, 2006; Fox et al., 2006; Shmuel and Leopold, 2008). These advances raise the possibility that FC mapping can reveal neural pathway abnormalities producing AVHs.

FC STUDIES OF AVHs USING fMRI DATA COLLECTED DURING TASK PERFORMANCE

Initial studies of AVH mechanisms utilizing FC incorporated different behavioral tasks during fMRI data acquisition. The first such study was reported by Lawrie et al. (2002), who compared eight patients with schizophrenia and 10 healthy controls using fMRI data collected during a sentence completion task. Correlations of BOLD activity time-course in the left

DLPC and left middle/superior temporal regions were reduced in patients with schizophrenia when compared to data from controls ($t = 1.8$, $df = 14$, $p < 0.05$ 1-tailed). Within the patient group, 3/8 patients were hallucinators. These patients had lower correlation scores relative to the non-hallucinating patients ($p < 0.05$). The authors hypothesized that these results reflected frontotemporal pathway disruptions that bring about AVHs. Along these lines, a leading hypothesis is that AVHs are instances of inner speech misidentified as non-self-due to a disruption of frontotemporal efference copy projections that ordinarily signal to sensory systems that actions (and thought) are self-generated (Feinberg, 1978; Frith and Done, 1988; Ford et al., 2007; Heinks-Maldonado et al., 2007; Jones, 2010).

In a second study, Shergill et al. (2003) studied eight hallucinating patients with schizophrenia and eight healthy control subjects. Two conditions were compared, self-paced inner speech generated once per second (repeating a single word, "rest") or the same word repeated once every 4 seconds. Relative to the control group, the patient group exhibited reduced correlation between left inferior frontal activity and activity in the right middle and superior temporal gyri, the right insula and a region encompassing the right parahippocampal, inferior temporal, and fusiform gyri. These findings were interpreted as indicating a source monitoring impairment with reduced information flow from frontal areas to posterior regions.

Using a different behavioral task involving perception of external speech, Mechelli et al. (2007) studied 10 hallucinating patients with schizophrenia, 10 non-hallucinating patients with schizophrenia and 10 healthy controls with fMRI. Stimuli consisted of pre-recorded single-word utterances. Some were recordings of words previously spoken by the subject, others were words generated by the subject during the same recording sessions but recorded by someone else, and a third set of stimuli were recorded by the subject, but pitch-shifted −0.4 semitones. Using dynamic causal monitoring applied to fMRI data, the functional impact of one region on another (referred to as "effective connectivity") was assessed relative to these three stimulus conditions. A total of five *a priori* cortical regions were defined—anterior cingulate, left inferior frontal, right inferior frontal, left posterior superior temporal, and right posterior temporal. This yielded a total of 20 ordered linkages that were analyzed for group differences. Using a corrected statistical threshold of 0.01, the impact of left superior temporal on anterior cingulate activity was found to be greater for non-self-spoken words compared to self-spoken words for healthy controls and non-hallucinating patients; however, this pattern was reversed for hallucinators, i.e., self-spoken speech produce greater effective connectivity along this pathway compared to non-self-spoken speech. These data, therefore, suggest some source monitoring alteration exhibited by hallucinators. That the direction of causal mapping for the critical pathway is posterior-to-frontal is not surprising given that: (1) this was a perceptual task; (2) non-self-produced speech requires auditory perceptual processing that is probably greater in scope than self-spoken words due to source identification processes. That this differential condition effect is reversed in hallucinators is of considerable interest. It is possible that somehow perceptual or source monitoring indicators of self vs. non-self-speech during perceptual processing are somehow switched. How this might happen remains uncertain.

RESTING FC STUDIES OF AVH PATHOPHYSIOLOGY

Resting or no-task FC fMRI studies have been used more recently to study AVH pathophysiology. These approaches offer the possibility of detecting spontaneous or baseline network interactions as predisposing factors leading to AVHs since no specific task is utilized during data collection. Four such FC studies of AVHs in patients with schizophrenia are outlined below:

Vercammen et al. (2010a) compared a relatively large sample of patients with active AVHs ($N = 27$) with healthy controls ($N = 27$) using resting state FC. FC was calculated for seed regions reflecting the left and right temporoparietal junction (TPJ) based on a previous study suggesting that both these cortical regions play an important role in the genesis of AVHs (Hoffman et al., 2007). Their patient group demonstrated subnormal left TPJ FC linking with the right homotope of Broca's area. There was no non-hallucinating patient group with schizophrenia in this study for comparison. However, within the group of hallucinators, more severe AVHs were associated with reduced FC linking the left TPJ seed region and the bilateral anterior cingulate and bilateral amygdala.

In a follow-up study, Vercammen et al. (2010b) rescanned 18 patients with schizophrenia after a six-day course of 1 Hz repetitive transcranial magnetic stimulation (rTMS) to the left TPJ or sham stimulation to the same location. FC relative to TPJ seed regions was assessed. Some studies have demonstrated that intervention has efficacy in reducing AVHs (Hoffman et al., 2005; Poulet et al., 2005). Although no corresponding changes were observed in FC following rTMS that at baseline were statistically associated with AVH severity, an increase in FC between the left TPJ and the right insula was observed in the group receiving active rTMS. This result is of interest given a number of studies finding activation in the insula associated with AVH events (for meta-analysis of activation studies of AVHs see Jardri et al., 2011). Moreover, these data suggest that low-frequency rTMS can enhance FC linking some regions.

A second study of AVHs utilizing resting FC was subsequently reported by Gavrilescu et al. (2010). Their group examined cross-hemisphere FC linking the primary and secondary auditory cortices in 13 patients with schizophrenia and AVHs, 13 similarly diagnosed patients without AVHs, and 16 healthy controls. Their selection of pathway was based on a prior neuropsychological study of AVHs suggesting abnormal transcallosal transfer of information in this patient group (Green et al., 1994). In the Gavrilescu study, separate FC assessments were computed for primary and secondary auditory cortex using regions of interest (ROI) determined from fMRI data collected while patients listened to words. This is a notable strength of the study insofar as this approach adjusts for the fact that localization of language functions is quite variable across subjects (cf. Ojemann, 1991). FC was estimated as the cross-correlation of primary and secondary auditory BOLD activity. Hallucinators demonstrated significant reductions in inter-hemispheric FC compared to the other two groups. As noted

by the authors, one limitation of their study is that this approach is not able to differentiate whether transcallosal disconnection was due to occurrence of hallucinations themselves or whether this finding reflected a vulnerability factor that is relatively sustained.

Raij et al. (2009) reported a third study of AVHs utilizing a measure related to FC based on at rest fMRI data. There was no comparison between hallucinating and non-hallucinating patient subgroups; instead shifts in coupling elicited by the on-off occurrences of hallucination events themselves were determined. These occurrences were signaled by patients during scanning. A total of 11 subjects who actively hallucinated during scanning were studied. Seed regions were defined in the left and right IFG. Specific ratings of level of reality and loudness of AVHs on an event-by-event basis were generated by each patient during scanning. Patient ratings of fluctuating levels of experienced reality of AVHs were found to correlate positively with hallucination-specific coupling linking the left IFG with bilateral auditory cortex, the right posterior temporal lobe, the middle right anterior cingulate cortex, the right ventral striatum, and the left nucleus accumbens. A correlation between hallucination reality and right IFG coupling with the right posterior temporal lobe was also detected. These findings, therefore, appeared to support the view that elevated FC along certain pathways makes AVHs worse. This view was further reinforced by our own studies described below.

FC STUDIES OF AVHs BY OUR GROUP

The first FC examination of AVHs reported by our group was incorporated into a larger study using fMRI methods to position rTMS in an attempt to curtail these experiences in the context of a clinical trial (Hoffman et al., 2007). Our primary finding was that left Wernicke's FC with the right homologue of Broca's area was strongly and negatively correlated with rTMS response to this region (Spearman-rank correlation $= -1.0$, $p < 0.001$) in patient group with continuous, non-stop hallucinations. Although based on a small number of subjects ($N = 6$), this correlation suggests that IFG/STG linkages reinforce pathophysiology, thereby rendering AVHs less reversible by rTMS.

Our group subsequently reported the largest FC study of AVHs to date, comparing 32 patients with schizophrenia-spectrum disorder and AVHs with similarly diagnosed patients without AVHs ($N = 24$) and healthy controls ($N = 23$; Hoffman et al., 2011). Non-hallucinating patients either never experienced AVHs, or if they did not within the five years prior to scanning. For the purposes of this study, FC was seeded from a bilateral Wernicke's region delineated according to BOLD activation detected when contrasting hallucination periods with non-hallucination periods that were signaled by a prior non-overlapping group of patients during fMRI scanning (Hoffman et al., 2008). This seed region was located in the left posterior superior temporal gyrus (STG) combined with a roughly homologous region in the right posterior STG and the neighboring middle temporal gyrus (MTG). This approach had not been previously employed in an FC study of AVHs, and potentially optimizes chances of accessing directly neurocircuitry involved in the genesis of these experiences. FC relative to this seed region was computed using methods involving low-pass filtering (frequency cutoff 0.1 Hz) and statistically removing effects of the average time-course of the slice in which the pixel was located, consistent with previous resting connectivity analyses (Hampson et al., 2002, 2006).

Unpublished pilot data based on another sample of subjects prompted us to predict that FC between the Wernicke's seed region and subregions of the left IFG would be elevated in the hallucinator group relative the non-hallucinator group and healthy controls. This prediction was assessed using a region-of-interest analysis. In addition, we undertook an exploratory voxel-based analysis to search for other sites showing group FC differences.

As predicted, Wernicke's-seeded FC with Brodmann Area 45/46 in the left IFG was significantly greater for hallucinating patients compared to non-hallucinating patients, but, contrary to our pilot data, not compared to healthy controls. The exploratory, voxel-based analysis did not reveal differences in any other brain region for bilateral Wernicke's-seeded FC comparing hallucinating and non-hallucinating patients after FDR correction (cut-off 0.05). However, a large cluster of subcortical voxels exhibited excessive FC relative to the Wernicke's seed region when comparing both patient groups with healthy controls following FDR correction. This cluster incorporated major components of the thalamus, midbrain, and putamen bilaterally.

In order to further probe the mechanism of AVHs, a seed region was defined in left IFG using a cut-off of 0.005 contrasting hallucinating and non-hallucinating patients. We furthermore divided the subcortical cluster described above into three ROIs, and calculated FC in a standard fashion, now relative to the left *IFG* seed region. One of these regions, the putamen, demonstrated excessive IFG-seeded FC when hallucinators were contrasted with non-hallucinating patients ($t(52) = 2.7$, $p = 0.009 \times 3 = 0.027$ after Bonferroni correction). IFG-seeded FC with the putamen, Wernicke's-seeded FC with the putamen, and Wernicke's-seeded FC with the IFG seed region were consequently summed together as a corticostriatal loop. This composite FC measure demonstrated a significant group effect ($F(2,76) = 9.84$, $p = 0.0002$), with hallucinators greater than both non-hallucinating patients and healthy controls, who were not different from each other (Duncan pairwise comparisons with $\alpha = 0.05$). Pooling data from the two patient groups, correlations between corticostriatal FC effects of antipsychotic drug dose (tallied as chlorpromazine equivalents) was assessed and found to be non-significant ($R = 0.08$). To determine if chronicity of illness contributed to our findings, correlation between network FC and number of hospitalizations was computed and found also to be non-significant ($R = -0.21$).

Relevant to the Vercammen et al. (2010a) findings, we found that FC was reduced between the bilateral Wernicke's seed region and the anterior cingulate in patients compared to controls; however, this finding did not differentiate hallucinating and non-hallucinating patient subgroups. Along similar lines, we found that FC between the bilateral Wernicke's seed region and a subregion in left IFG (BA47) to be reduced in patients. This finding is consistent with other studies demonstrating partial frontotemporal disconnection in hallucinators (Lawrie et al., 2002; Shergill et al., 2003). However, these FC data in our study

also did not differentiate hallucinating and non-hallucinating patients. Therefore, our FC data, based on a larger sample of hallucinating patients with well-matched comparison groups of non-hallucinating patients and healthy controls, suggest overall that these corticocortical pathways are unlikely to play a primary mechanistic role in the generation of AVHs.

We found instead that the only pathway demonstrating hyperconnectivity differentiating hallucinators and healthy controls—at least in terms of the seed regions selected—was between the putamen and the bilateral Wernicke's seed region. However, in terms of specificity of findings, a parallel group difference was also detected between non-hallucinating patients with schizophrenia. How can one make sense of these FC findings, considered as whole?

One clue is that the putamen appears to play a critical role in initiating language representations (Price, 2010). Moreover, FC linking the putamen to diverse cortical regions plays a critical role in determine whether external auditory stimuli are experienced as conscious percepts (Mhuircheartaigh et al., 2010) Excessive functional coordination linking this region with the Wernicke's seed region in patients with schizophrenia could, therefore, generate an overabundance of potentially conscious language representations. Intact FC in the other two legs of corticostriatal loop (Wernicke's ↔ left IFG, and left IFG ↔ putamen) appeared to allow this disturbance (common to schizophrenia overall) to be expressed as a conscious hallucination of speech. *Disruption in one or both of these linkages, in essence, appears to protect patients from experiencing overabundant, spontaneous language representations as (spurious) externalized percepts of spoken speech*. It is generally assumed that disconnection leads to greater functional disturbance. However, our data support a more complex view whereby hyperconnectivity intrinsic to one component in a functional loop may be counterbalanced by hypoconnectivity in other components of that loop.

These study results are consistent with a recent study demonstrating that treatment with second-generation antipsychotic medications in patients with schizophrenia produces widespread *reductions* in FC that may be related to their therapeutic effects (Lui et al., 2010). The prediction of this study is that curtailment of connectivity in any of the three legs of the corticostriatal loop (Wernicke's ↔ left IFG, and left IFG ↔ putamen or putamen ↔ Wernicke's) would produce a reduction in AVHs.

These findings challenges inner speech models of AVHs based on disconnection of monitoring processes or efferent copy signaling (for review see Jones, 2010; see also Heinks-Maldonado et al., 2007) since no disconnected pathway is identified as a primary causal factor. These findings also challenge acoustic memory explanatory models (Jones, 2010) since involvement of medial temporal regions ordinarily involved in these memory processes was not linked with AVH vulnerability. However, these findings are consistent with a speech perception network activity model of AVHs termed "social deafferentation" (Jones, 2010). This model is based on the fact that these patients, prior to onset of psychosis, are generally in a state of social withdrawal (for original description of this model see Hoffman, 2007). Hallucinated speech could then a brain response to "fill in the blank" of relatively absent conversational discourse in the real world given that the human brain is highly dedicated to processing and understanding spoken language ordinarily. The social deafferentation model predicts lowered threshold-to-consciousness of language representations analogous to other types of hallucinations generated from sensory deafferentation states (such as visual deprivation) where there is also lowering of threshold-to-consciousness. Hyperconnectivity linking the putamen and Wernicke's area could be the means whereby lowered threshold-to-consciousness of conversational language representations occurs in patients with schizophrenia.

DISCUSSION

The FC studies reviewed above have produced divergent results. Reasons for this divergence are likely numerous.

First, the task-related FC studies outlined above each utilized different behavioral tasks and utilized small numbers of subjects, making more general conclusions difficult. It is also hard to integrate findings across the studies reviewed above since, task-based FC reflects different neural processes compared to no-task FC. This conundrum is suggested by a meta-analysis reported by Kompus et al. (2011), who pooled results fMRI and PET activation studies of spontaneous AVH events in parallel with results of activation studies conducted utilizing external auditory stimuli in patients with these symptoms. A paradox was detected: robust, spontaneous activation was detected in the left primary auditory cortex and other regions concurrent with hallucination events, even though responses to external auditory stimuli were subnormal for hallucinators. The authors suggested that this discrepancy was due either to an attentional bias toward internal events, or some failure of a default network to deactivate when auditory processing neurocircuitry is engaged by external stimuli. An analogous situation may hold for FC ascertained along some pathways: engagement in a listening task (see for instance Mechelli et al., 2007) may elicit subnormal activated FC in hallucinators compared to controls—possibly due to a failure to deactivate default processing, whereas spontaneous FC in hallucinators along similar pathways may still be normal or supranormal.

Another source of study outcomes differences derives from the fact that, when calculating FC, data analytic methods are applied in order to minimize spurious sources of covariance such as breathing, cardiac pulse, and other brain-wide shifts in activation. These methods varied considerably from one study to the next, which will lead to very different results.

One serious limitation is that only three of eight FC studies reviewed above compared hallucinating and non-hallucinating patients (Mechelli et al., 2007; Gavrilescu et al., 2010; Hoffman et al., 2011), which is an important test of any mechanistic model of this symptom.

Two of three no-task FC studies of AVHs have highlighted disconnection as a factor, one considering cross-hemispheric linkages (Gavrilescu et al., 2010), and the other (Vercammen et al., 2010a) considering a linkage similar to that considered by Mechelli et al. (2007). However, implications of the Vercammen et al. findings are uncertain since the FC linkage correlating with hallucination severity was not the FC linkage that was

abnormal in the patient group compared to healthy controls. The Vercammen et al. study could be interpreted as indicating that reduced left temporoparietal ↔ right Broca's FC is the *primary* abnormality, with relative reductions in FC linking the former with bilateral anterior cingulate and the amygdala being *permissive* in allowing AVH experiences to emerge. Our data did not confirm these FC relationships and group differences. Perhaps the reason for this discrepancy is that our definition of a temporoparietal seed region was different, involving Wernicke's areas proper plus a right homologous pooled site based on a prior fMRI activation study of AVH events (Hoffman et al., 2008). Another uncertainty regarding the Vercammen et al. findings is that the functional capacities of right Broca's area are not well understood. This region appears to have some residual linguistic processing capacity elicited by tasks such as word reading that can be detected with neuroimaging following left IFG lesions (Rosen et al., 2000). How disconnection of this functional capacity relative to left TPJ might increase vulnerability to AVHs is not clear.

In contrast, our corticostriatal FC findings and those reported by Raij et al. (2009) suggest that heightened FC along certain pathways plays an important role in the genesis of AVHs. A hybrid model consequently has been proposed by one of us (Ford and Hoffman, 2012) whereby "locked in" speech perception neurocircuitry dynamics arising from network hyperconnectivity both: (1) lowers threshold-to-consciousness of language representations, and (2) overrides corollary discharge signals from frontal areas to produce a source monitoring defect; in this scenario, both factors contribute to the genesis of hallucinatory experience. A related model has been proposed by Hugdahl (2009), whereby perceptual neurocircuitry is responsible for key aspects of hallucinatory experience, with a failure of top-down processing amplifying a specific (experiential, etc.) dimension, namely the sense that the experience derives from an external source.

It is noteworthy that disconnection along some pathways is not inconsistent with hyperconnectivity along other pathways; in fact the two types of findings may be related. For instance, hyperconnectivity linking regions A and B will tend to depress indirectly FC linking regions B and C. The reason for this is that elevating variance detected in B referable to A will tend to mask variance in B referable to C—thereby depressing FC between the latter two regions. Moreover the opposite is also true: decreasing variance detected in B referable to A could *unmask* variance in B shared with C—hereby increasing FC linking the latter two regions.

In terms of future studies, we believe that a numerous refinements in method are indicated to clearly demarcate the mechanism of AVHs.

First, future FC studies need to consider specific loops and networks, not single pathways.

Second, complex data acquisition protocols applied to same subjects should be used to directly compare and contrast competing explanatory models of AVHs. For instance, we are now undertaking a study that examines resting FC and FC during the inner speech task described by Shergill et al. (2003) to ascertain the relationship between corticostriatal loop abnormalities and efference copy disconnection.

Third, it is critically important to more clearly differentiate between findings reflecting sustained vulnerability factors leading to AVHs versus processes occurring simultaneous and downstream of actual occurrences of AVHs. An examination of our corticostriatal FC data, for instance, included consideration of effect of objective rate of hallucinations for those patients ($N = 10$) signaling these events with button-presses during scanning. A promising correlation between corticostriatal loop FC and hallucination frequency was detected, although not statistically significant (Spearman rho $= 0.50$, $p = 0.11$), possibly due to the small number of subjects who were able to complete this task. Our hypothesis is that there is a dynamic process at play whereby baseline elevations in corticostriatal FC (reflecting a sustained vulnerability factor) lead to further transient increases in FC that occur episodically and correspond to hallucination experiences themselves. Methods capable of more fine-grained analysis of temporal time-course, such as EEG or MEG would be helpful to more fully clarify this issue by looking for synchronization "spikes" simultaneous with occurrence of AVH events.

Fourth, these studies will likely be advanced if different phenomenological types of AVHs are ascertained. Our experience with this population suggests at least three subtypes of AVHs. The first is the "standard" type, where hallucinations are intermittent, spontaneous, with clear breaks between events. This is the dominant form of hallucination among patients with schizophrenia, and they generally respond to currently available treatments, including medication and/or rTMS. However, there are two other hallucination subtypes that we have found to be much more treatment-resistant, suggesting a somewhat different mechanism. The first are patients whose AVHs occur continuously during wakefulness (i.e., no intervening "silent" periods). These patients prompted our first FC study that was combined with rTMS, and produced a somewhat different pathophysiological model highlighting interactions between posterior temporal regions and the right homologue of Broca's area as critical in generating AVHs (Hoffman et al., 2007). The third type of AVHs consists primarily of perceptual transformations of actual spoken speech generated in the environment with some phonetic unclarity, such as mumbled speech in a crowd, rapid speech on the television, or song. These instances of AVHs, which result in spurious, self-referential verbal percepts, seem clearly to arise from aberrant and excessive top-down processing, and are worthy of targeted study in their own right. Other critical dimensions are the overall sense of reality of AVHs (cf. Raij et al., 2009), perhaps best characterized by the degree that patients differentiate these experiences from their own inner speech (Hoffman et al., 2008). A more precise characterization of AVH subtypes may sharpen characterization of corresponding neurocircuitry.

Fifth, it will be important to ascertain whether the connectivity abnormalities delineated by such studies in patients with schizophrenia produce specific cognitive or language processing impairments outside of producing AVHs.

Overall these FC studies have raised important questions regarding the mechanism of AVHs which are addressable by new, improved study designs.

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Neuroimaging of voice hearing in non-psychotic individuals: a mini review

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Auditory verbal hallucinations (AVH) or "voices" are a characteristic symptom of schizophrenia, but can also be observed in healthy individuals in the general population. As these non-psychotic individuals experience AVH in the absence of other psychiatric symptoms and medication-use they provide an excellent model to study AVH in isolation. Indeed a number of studies used this approach and investigated brain structure and function in non-psychotic individuals with AVH. These studies showed that increased sensitivity of auditory areas to auditory stimulation and aberrant connectivity of language production and perception areas is associated with AVH. This is in concordance with investigations that observed prominent activation of these areas during the state of AVH. Moreover, while effortful attention appears not to be related to AVH, individuals prone to hallucinate seem to have an enhanced attention bias to auditory stimuli which may stem from aberrant activation of the anterior cingulated regions. Furthermore, it was observed that decreased cerebral dominance for language and dopamine dysfunction, which are consistently found in schizophrenia, are most likely not specifically related to AVH as these abnormalities were absent in healthy voice hearers. Finally, specific aspects of AVH such as voluntary control may be related to the timing of the supplementary motor area and language areas in the experience of AVH.

Keywords: auditory verbal hallucinations, non-psychotic individuals, psychosis, schizophrenia, fMRI, PET, EEG, DTI

INTRODUCTION

In contemporary Western societies auditory verbal hallucinations (AVH) or "voices" are generally considered an aspect of disease (al-Issa, 1995). Indeed, AVH are frequently observed in individuals with a neurological, neurodegenerative, or psychiatric disorder (Aleman and Laroi, 2008). Moreover, these hallucinations are observed in ∼10–15% of healthy, i.e., non-psychotic, individuals in the general population (Tien, 1991; Sommer et al., 2008; Beavan et al., 2011). AVH are even more common during periods of partial wakefulness, i.e., when falling asleep (hypnagogic hallucinations) or during waking (hypnopompic hallucinations). AVH are, however, most common in schizophrenia, in which they occur with an average prevalence of 70% (Sartorius et al., 1986).

While AVH are not associated with distress in non-psychotic individuals, they can seriously disrupt social functioning in psychotic patients (Nayani and David, 1996; Daalman et al., 2011). At present, the primary treatment for AVH in psychiatric patients consists of antipsychotic medication which is frequently combined with cognitive behavioral therapy. These hallucinations do, however, not respond to pharmaceutical intervention in 25–30% of patients, stressing the need for development of new treatment options (Shergill et al., 1998). This is, at present, hampered by the fact that the pathophysiology of AVH remains largely unknown.

Over the last decades a considerable number of studies aimed at elucidating the neurobiological mechanism of AVH in schizophrenia patients. Most of these can be divided into "symptom-capture" (a.k.a. "state" studies) on the one hand and "trait" investigations on the other hand (Kühn and Gallinat, 2010). The first group of studies investigated the neural signature of AVH and revealed that AVH-related brain activation can be observed in frontal and temporoparietal language areas as well as in the parahippocampal region (Jardri et al., 2010; Kühn and Gallinat, 2010). Although these studies provide a helpful start at understanding what happens in the brain during AVH, they do not provide information about brain mechanisms predisposing a person to experience AVH. The latter can be provided by trait studies that focus on comparing brain activation between individuals with and without AVH. Previous studies showed that the propensity to hear voices may be associated with a number of factors including decreased left cerebral dominance for language (Levitan et al., 1999; Sommer et al., 2001; Weiss et al., 2006; Hugdahl et al., 2007), dysfunctional connectivity of frontal and temporoparietal language regions (Frith et al., 1995; Spence et al., 2000; Ford et al., 2007; Kühn and Gallinat, 2010), decreases in psychophysiological measures of effortful attention (Havermans et al., 1999; Turetsky et al., 2000), and dopamine dysfunction. It should, however, be noted that results are inconsistent.

While all of these factors may be involved in the genesis of AVH, a key limitation is that most of these studies were conducted in patients with schizophrenia. Schizophrenia is a complex syndrome comprising positive, negative, and cognitive symptoms. In addition, schizophrenia patients typically use antipsychotic medication. As a result, observed deviations may not be specifically

related to AVH, but rather to another symptom or to general cognitive dysfunction observed in these patients. To elucidate if AVH are indeed specifically related to the aforementioned factors, they could be studied in (relative) isolation. Interestingly, previous studies have shown that AVH in the non-psychotic population frequently occur in the absence of other psychiatric symptoms and medication-use (Tien, 1991; Sommer et al., 2008; Beavan et al., 2011). These subjects thus provide an ideal opportunity to investigate a more isolated form of AVH.

In this review, neuroimaging studies in non-psychotic individuals with AVH will be summarized. While different studies used different terminology for these individuals including non-clinical (Linden et al., 2011), non-psychotic (Diederen et al., 2010b, 2011; van Lutterveld et al., 2010; de Weijer et al., 2011), healthy (Howes et al., 2012), and hallucination-prone individuals (Lewis-Hanna et al., 2011), they will be termed non-psychotic individuals with AVH in this review. In the next section both state and trait studies will be described in detail. In addition to these studies which were conducted in individuals who present with non-evoked AVH, two studies will be discussed in which AVH were evoked in hallucination-prone individuals using hypnosis or conditions of degraded stimulus information (Szechtman et al., 1998; Barkus et al., 2007).

STATE STUDIES 1: NON-EVOKED HALLUCINATIONS

PSYCHOTIC AND NON-PSYCHOTIC INDIVIDUALS

A recent neuroimaging study into the state of AVH in non-psychotic individuals with AVH compared brain activation during AVH between 21 non-psychotic and 21 psychotic subjects (Diederen et al., 2011). The rationale was that if AVH are caused by comparable mechanisms in both groups, one should observe a similar pattern of AVH-related brain activation. Indeed, the two groups displayed common areas of activation in the absence of any significant differences. These areas consisted of the bilateral inferior frontal gyri, insula, superior temporal gyri, supramarginal gyri and postcentral gyri, left precentral gyrus, inferior parietal lobule, superior temporal pole, and right cerebellum. Activation of these areas has been interpreted to reflect language and motor processes (perhaps as a result of balloon-squeezes used to indicate the AVH) in the experience of AVH.

HALLUCINATIONS VS. IMAGERY

More insight into the role of frontal and temporoparietal regions in the experience of AVH was provided by a recent study which compared AVH-related brain activation in seven non-psychotic individuals with AVH to imagery in 7 healthy subjects who did not present with AVH (Linden et al., 2011). This study revealed that both processes activated the supplementary motor area and bilateral frontotemporal language regions including the human voice area. This suggests that hallucinations as well as imagery are associated with an auditory percept. In addition, a difference in timing of brain regions was found for the two processes. While activity of the supplementary motor area preceded that of auditory areas during imagery, activation of these areas occurred instantaneously for AVH. The authors concluded that the different timing of the supplementary motor area is associated with the absence of control over the AVH in their group of individuals.

STATE STUDIES 2: EVOKED HALLUCINATIONS

HALLUCINATIONS, HEARING, AND IMAGERY DURING HYPNOSIS

Imagery and AVH were also compared in an early study in which eight subjects hallucinated under hypnosis (Szechtman et al., 1998). In addition to AVH and imagery, brain activation during actual hearing was investigated in the same individuals as well as in six highly hypnotizable controls, without the ability to hallucinate under hypnosis, using PET. Both hallucinations and auditory stimulation, but not imagery, activated the right anterior cingulate area. Moreover, hallucination-related brain activation of this area correlated strongly with subjects' ratings of externality and clarity of the heard voice. Interestingly, hearing and imagery did not correlate with significant anterior cingulated activation in the control group of non-hallucinators from which the authors concluded that inappropriate activation of this region may lead self-generated thoughts to be experienced as external. It is, however, important to note that these results are not in line with the study by Linden et al. (2011) who found a similar pattern of activation during imagery and hallucinations. This might be related to the difference in evoked and non-evoked AVH.

HALLUCINATIONS AND HEARING DURING STIMULUS DEGRADATION

Using a different method to elicit hallucinations in hallucination-prone individuals Barkus et al. (2007) presented subjects with episodes of white noise during which a voice was presented part of the time. Subjects had to indicate if they had heard a voice during the noise resulting in a number of hits, but also "false alarms" which were used as a model for hallucinations. Eight of 68 subjects who reported hearing a voice when none was present repeated the task during functional imaging. Patterns of activation during false alarms showed activation in the right middle temporal gyrus, bilateral fusiform gyrus, and the right putamen. As this pattern of activation is rather similar to activation observed during AVH in patients the authors concluded that AVH in non-clinical samples appear to be mediated by similar patterns of cerebral activation as found during hallucinations in schizophrenia. Importantly, this is in line with the study by Diederen et al. (2011). For an overview of state studies on AVH see **Table 1**.

TRAIT STUDIES

PSYCHOPHYSIOLOGICAL PARAMETERS OF ATTENTION

The first trait study in non-psychotic individuals with AVH investigated if AVH are specifically associated with dysfunction in psychophysiological parameters of attention (van Lutterveld et al., 2010). In this EEG study, three event related potentials (ERPs) were examined with an auditory oddball paradigm in 18 non-psychotic individuals with AVH and 18 controls. While no significant differences were found for mismatch negativity, P300 amplitude was increased in the AVH group as compared to controls, reflecting superior effortful attention. A trend in the same direction was found for processing negativity. As the non-psychotic individuals with AVH showed increased rather than decreased psychophysiological measures of effortful attention, these results suggest that the decrease in EEG measures of effortful attention observed in schizophrenia patients is not related to the tendency to hallucinate.

Table 1 | Symptome capture studies on AVH in non-psychotic individuals.

Author	Subjects	Design	Method	Key neuroimaging results
NON-EVOKED				
Linden et al. (2011)	7 Non-psychotic subjects w. AVH 7 Non-hallucinator controls	Brain activation during AVH vs. imagery	fMRI	Similar act. AVH and imagery: ↑ B voice area (STS), IFG, cerebellum, planum temporale, prefrontal, inferior parietal lobules, thalami, and L motor cortex Group diff.: in controls(imagery) ↑ SMA preceded ↑ auditory areas, in hallucinators activity occurred at same time
Diederen et al. (2011)	21 Non-psychotic subjects w. AVH 21 Psychotic patients with AVH	Brain activation during AVH	fMRI	Similar act.: ↑ B IFG, insula, STG, SMG, postcentral gyri, L precentral gyrus, inferior parietal lobule, superior temporal pole, and right cerebellum No sign. differences between groups
EVOKED				
Szechtman et al. (1998)	8 Healthy volunteers w. AVH under hypnosis 6 Healthy volunteers w.o. AVH under hypnosis	Brain activation during AVH, hearing, and imagining	PET	AVH and Hearing (not imagining): ↑ R anterior cingulate in hallucinating subjects In non-hallucinating subject: no sign. activation in anterior cingulate
Barkus et al. (2007)	8 High hallucination-prone subjects	AVH elicited using a signal detection task Brain activation during false alarms (AVH), rejections (voice present but not detected), and hits (voice correctly detected)	fMRI	False alarms – correct rejections: ↑ R MTG, B fusiform gyrus, and R putamen False alarms-hits: ↑ R SFG, MFG, L cingulate gyrus, MTG, cerebellum, and B STG

w., with; w.o., without; AVH, auditory verbal hallucinations; fMRI; functional magnetic resonance imaging; PET, positron emission tomography; B, bilateral; L, left; R, right; STS, superior temporal sulcus; IFG, inferior frontal gyrus; SMA, supplementary motor area; STG, superior temporal gyrus; SMG, supramarginal gyrus; MTG, middle temporal gyrus; SFG, superior frontal gyrus; MFG, middle frontal gyrus.

LANGUAGE LATERALIZATION

An influential theory on AVH poses that AVH result from decreased left cerebral dominance for language, i.e., language lateralization (Sommer and Diederen, 2009). To test this hypothesis a second trait study compared language lateralization between 35 non-psychotic individuals with AVH and 35 psychotic patients as well as 35 healthy control subjects (Diederen et al., 2010b). While the patients displayed decreased language lateralization, this could not be observed in the non-psychotic individuals with AVH. It is therefore not considered likely that these hallucinations result from decreased cerebral dominance for language.

FRONTOTEMPORAL CONNECTIVITY

The most influential contemporary model poses that AVH occur due to a failure to recognize self-generated inner speech (Frith et al., 1995; Spence et al., 2000; Ford et al., 2007). This is hypothesized to result from dysfunctional integration of frontotemporal language production and perception areas which are connected via the arcuate fasciculus. To address this hypothesis, a recent study compared tract integrity of the arcuate fasciculus and three other white matter tracts between 35 non-psychotic individuals with AVH, 35 schizophrenia patients with AVH, and 36 controls (de Weijer et al., 2011). While patients showed abnormalities in multiple white matter tracts, the healthy individuals with AVH only showed microstructural aberrations in the arcuate fasciculus, which is in line with the inner speech model of AVH.

AUDITORY ATTENTION AND STIMULATION

With a primary focus on auditory processes Lewis-Hanna et al. (2011) investigated 12 individuals who were prone to sleep-related (i.e., hypnagogic and hypnopompic) hallucinations. The authors examined speech-evoked brain activation as well as modulation of brain activation by auditory attention using fMRI. Hallucinating individuals demonstrated greater speech-evoked activation in the left supramarginal gyrus compared to a control group of similar sample size. In addition, directing attention towards the auditory modality was associated with greater activation of the anterior cingulate gyrus in the hallucinator group. The authors concluded that hallucination-proneness is associated with increased sensitivity of auditory areas to auditory stimulation, which might arise due to an enhanced attentional bias from the anterior cingulate gyrus.

DOPAMINE FUNCTION

Another process associated with the origin of AVH is dopaminergic dysfunction which has been frequently observed in psychotic patients (Laruelle and Abi-Dargham, 1999; Howes et al., 2007). Thus far, it is not clear if this dysfunction is related to psychosis in general or to a specific symptom. To elucidate if such a specific association with AVH exists, Howes et al. (2012) compared dopamine synthesis capacity in 16 non-psychotic individuals with AVH to 16 controls and showed that no significant difference could be observed between the groups (Howes et al., 2012). The authors concluded from this that altered dopamine synthesis capacity is

Table 2 | Trait studies on AVH in non-psychotic individuals.

Author	Subjects	Design	Method	Key neuroimaging results
van Lutterveld et al. (2010)	18 Non-psychotic subjects w. AVH 18 Non-hallucinator controls	P300 waveforms, PN, and MMN with an auditory oddball paradigm	EEG–ERP	↑ P300 amplitude in non-psychotic subjects ↑ PN amplitude (trend-level) in non-psychotic subjects No sign. group difference MMN
Diederen et al. (2010b)	35 Non-psychotic subjects w. AVH 35 Psychotic patients w. AVH 35 Non-hallucinator controls	Covert verbal fluency task	fMRI	↓ Language lateralization in patients, not non-psychotic subjects w. AVH
de Weijer et al. (2011)	35 Non-psychotic subjects w. AVH 35 Schizophrenia patients w. AVH 36 Non-hallucinator controls	Tract integrity of the AF and control tracts (CST, CGL, and UF)	DTI and MTI	↑ MTR in L AF in non-psychotic individuals and patients w. AVH ↑ MTR R AF in patients ↓ FA in L AF, R CST, and B UF in patients
Lewis-Hanna et al. (2011)	12 Non-pyschotic subjects w. auditory HG/HP hallucinations 12 Non-hallucinator controls	Speech-evoked brain activation and selective attention paradigm (auditory/visual)	fMRI	↑ Speech-evoked act. L SMG in hallucinating group ↑ Anterior cingulate activity when directing attention to auditory (vs. visual) modality in hallucinating subjects
Howes et al. (2012)	16 Non-subjects w. AVH 16 Non-hallucinator controls	[18F]-DOPA PET	PET	No significant group difference in striatal dopamine synthesis capacity

w., with; AVH, auditory verbal hallucinations; HG, hypnagogic; HP, hynopompic; PN, processing negativity; MMN, mismatch negativity; AF, arcuate fasciculus; CST, cortico spinal tract; CGL, cingulated; UC, uncinate fasciculus; EEG, electroencephalography; ERP, event related potentials; fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging; MTI, magnetic transfer imaging; PET, positron emission tomography; B, bilateral; L, left; R, right; SMG, supramarginal gyrus.

unlikely to underlie (sub-clinical) hallucinations. For an overview of trait studies on AVH see **Table 2**.

DISCUSSION

In summary, these studies show that while decreased cerebral dominance for language and dopamine dysfunction are presumably not specifically related to AVH, increased sensitivity of auditory areas to auditory stimulation and aberrant connectivity of language production and perception areas is particularly associated with these hallucinations. This is in concordance with state studies which observed prominent activation of these areas during the state of AVH (Jardri et al., 2010; Kühn and Gallinat, 2010). Moreover, while effortful attention appears not to be related to AVH, individuals prone to hallucinate seem to have an enhanced attentional bias to auditory stimuli which may stem from aberrant activation of the anterior cingulated regions. Furthermore, specific aspects of AVH such as voluntary control may be related to the timing of the supplementary motor area and language areas in the experience of AVH.

In addition, these studies imply that investigating non-psychotic individuals with AVH provides an excellent model to disentangle which dysfunctions may be specifically related to these hallucinations. Future studies should therefore focus on investigating additional processes which have been associated with AVH, including for instance the role of top-down processes and anatomical integrity of language regions. A second aim of future studies should consist of investigating brain activation preceding AVH as such studies in psychotic patients showed that AVH are most likely instantiated by memory retrieval (Hoffman et al., 2008, 2011; Diederen et al., 2010a). Finally, future studies could elucidate how specific AVH-characteristics are associated with brain activation. As psychotic and non-psychotic individuals display both differences and similarities with respect to specific AVH-characteristics it would be ideal to combine these groups in such a study (Daalman et al., 2011).

METHODOLOGICAL CONSIDERATIONS

These studies should be interpreted with caution as individuals with both evoked and non-evoked AVH participating in most of these studies were highly selected. Furthermore, a limitation is that most of the state studies included only a small number of subjects, i.e., typically less than ten per group. In addition, one may wonder if these individuals should indeed be considered non-psychotic. If strict Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria for axis I were applied, all subjects with non-evoked and non-sleep-related AVH would meet criteria for psychosis not otherwise specified (NOS) as all participants met the criterion persistent hallucinations, which in itself is sufficient for this classification. However, the DSM general terms state that a person has to be bothered by his symptoms and/or dysfunction on social, psychological, and professional domains should be present in order to make a diagnosis. The fact that the hallucinating subjects participating in the studies described showed no social, affective, or professional dysfunction, were not bothered by the AVH and were not in need of treatment, indicates that the diagnoses psychosis NOS is clinically inappropriate (Sommer et al., 2008).

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How do auditory verbal hallucinations in patients differ from those in non-patients?

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Auditory verbal hallucinations (AVHs) are experienced by individuals with various clinical diagnoses, such as psychosis, but also a significant minority of healthy individuals from the general population may experience them. Although much research has been carried out the past few decades, the mechanisms and factors underlying the emergence of AVHs is still poorly understood. One way of clarifying this issue involves comparing AVHs in patient and non-patient populations. In particular, differences between these groups will provide important information concerning the emergence of AVHs. After a general presentation and discussion of the notion of a continuum hypothesis, studies comparing patients with non-patients experiencing AVHs will be reviewed. This will comprise studies examining the phenomenological characteristics of AVHs in addition to neuroimaging and cognitive studies. Although we are beginning to elucidate important differences on a phenomenological level between these two types of AVHs, far too few studies have directly compared patient and non-patient AVHs in terms of underlying cerebral correlates and cognitive mechanisms. Nevertheless, and based on recent research on phenomenological differences, two issues stand out that need to be addressed, namely, the highly negative emotional content of AVHs in patients and the early onset of AVHs in non-patients populations. Suggestions for future research will be discussed.

Keywords: hallucinations, auditory verbal hallucinations, voice-hearing, continuum, dimension, phenomenology, cognition, neuroimaging

INTRODUCTION

Hallucinations, or perceptions in the absence of stimuli, may occur in any sensory modality such as auditory, visual, olfactory, gustatory, or tactile. They are very common in individuals with schizophrenia, but may also occur in those suffering from various other psychopathological (e.g., mood disorders, Post-traumatic Stress Disorder, Substance abuse, Borderline Personality Disorder) or neurological (e.g., Dementia, Parkinson's disease, epilepsy) disorders. Studies have furthermore shown that a significant minority of otherwise healthy persons may also experience hallucinations (for reviews of this literature, see Aleman and Larøi, 2008 and Beavan et al., 2011).

Auditory hallucinations represent a particularly rich and varied phenomenology. They involve the perception of a large array of sounds, which, when involving voices, are referred to as auditory verbal hallucinations (AVHs). AVHs are the main focus of the present article as this type of hallucination has been the most often examined in the literature in general, but also in studies comparing hallucinations in clinical groups compared to those experienced by non-clinical or healthy persons.

Despite a significant increase in studies investigating AVHs in the past few decades (cf. Aleman and Larøi, 2008), they remain poorly understood, in particular regarding underlying mechanisms and factors involved in the development or emergence of AVHs. There exist a number of approaches that can be adopted in order to better elucidate this process. One particularly fruitful recent approach to resolving this issue has been the use of combined epidemiological and longitudinal studies (i.e., following up a representative group of individuals from the general population over time). This line of research can, for example, investigate the nature of the transition from a non-clinical hallucination to a clinical hallucination (i.e., the latter referring to hallucinations in individuals who are in need of professional help for these experiences) and consequently say something about who needs treatment for their AVHs, and why. Two main psychological mechanisms seem to be involved in this. First, response to abnormal experience, such as AVHs, seems to be cognitively mediated by beliefs or appraisals (Garety et al., 2001). That is, the mere experience of AVHs itself might not lead to full-blown psychotic hallucinations, but, for instance, attributing the AVHs to an external malevolent source and giving it personal significance does. Another important determinant of the transition to clinical states may be the level of functional coping that the person mobilizes in the face of stressful experiences such as AVHs. Active coping strategy such as using problem-solving, seeking help, and distraction, seems to generate control over the experiences. In contrast, more passive coping strategies such as going along with and indulging in the content of hallucinations, isolating oneself, getting involved in non-specific activities, do not generate more control over the experiences.

Another way of clarifying the developmental trajectory of AVHs involves the detailed assessment of changes in mental experiences that occur before AVHs develop, especially during early

(i.e., prodromal) phases of psychosis. A number of changes can be observed that involve a general perceived change in the stream of thoughts of the person (e.g., thoughts no longer shift smoothly and effortlessly from one moment to the next). Individuals may also report that thoughts feel anonymous or spatialized, may acquire a quasi-sensorial concreteness or are experienced as deprived of the tag of "mineness" and familiarity (cf. Larøi et al., 2010; Raballo and Larøi, 2011).

THE CONTINUUM HYPOTHESIS

Another fruitful approach to help elucidate the emergence of AVHs involves comparing AVHs present in persons with psychosis compared with those AVHs experienced by non-clinical persons or non-patients. As with the combined general population and longitudinal research described above, this line of research provides ways of better differentiating between problematic AVHs that call for treatment (e.g., that are associated with a psychosis diagnosis), and those that do not.

Studies show that some 10–15% of the healthy population at times experience AVHs (Sommer et al., 2010). In a recent review of the literature (Beavan et al., 2011), which included 17 studies that have examined the prevalence of AVHs in the adult general population, the authors report prevalence rates ranging from 0.6 to 84%. The great majority of the studies included in this review came from Western countries (European countries, the USA) with the exception of two studies from New Zealand and the Philippines. This high degree of variation in reports of AVHs reflects differences in studies in terms of methodology and design (definitions of hallucinations, how items are formulated, the context of the study, participants' socio-demographic characteristics, etc.). For instance, high levels of AVHs prevalence are related to definitions being too broad (e.g., "hearing vocal sounds" or "hearing a voice saying a few words"), periods being too unspecific (e.g., "have you ever experienced . . . "), or the inclusion of very common experiences (e.g., "heard own name in a shop"). Moreover, in the few studies that investigated differences in the frequency of hallucinatory experiences among different ethnic groups, it was found that some ethnic groups are more likely than others to report hallucinatory experiences. For example, higher rates were reported for Brazilian, Russian, Caribbean, Hispanic, and Black respondents compared to Western, Caucasian individuals. Other factors were also identified that play a role in the variation of rates such as gender (higher in women) and loss (e.g., decease of a loved one) and trauma (e.g., bullying, sexual abuse).

Nevertheless, these types of findings suggest that hallucinations in general, and AVHs in particular, may be considered as dimensional phenomena lying on continua with normal experiences (Johns and van Os, 2001), and that there are no clear qualitative differences but rather quantitative differences between normality and pathology. It is perhaps preferable to refer to this as a continuum "hypothesis" or "view" (and not a model or theory) as there is still debate concerning the true nature of this continuum, and therefore, hopefully this debate will continue in years to come (David, 2011) as an uncritical acceptance of the continuum hypothesis is clearly to be avoided (Badcock and Hugdahl, 2012).

In this context, it is also important to note that one can distinguish between at least two types of continua (Bentall, 2003; David, 2011):

(1) A continuum of experience, that is within an individual, and which suggests that different kinds of experience (e.g., vivid daydreams, intrusive, and vivid thoughts) may be related to AVHs. This continuum may vary, for instance, from normal thoughts, to intrusive and vivid thoughts, to thoughts resembling voices, and finally to AVHs.
(2) A continuum of risk, which is across several individuals, and indicates that people differ in their proneness to have AVHs experiences, and similarly also in their level of risk to develop problematic or "clinical" AVHs. This continuum may vary, for instance, in terms of frequency—from those with no hallucination-proneness (e.g., that have never had an AVH or AVH-like experience in their lives), to those who once or sometimes have had such an experience, to those who have it quite frequently, and finally to those who have it very frequently. Similarly, persons on this continuum vary in terms of risk: from those with no risk to develop clinical AVHs at one extreme, to those with a very high risk to do so at the other end.

Thanks to a significant body of studies that has appeared the past few years, it is now possible to attempt to characterize those persons (i.e., those 10–15% from the general population) who lie on this continuum of risk. At the one end of the continuum are those healthy individuals who experience AVHs very rarely, perhaps often under specific conditions (such as after sleep deprivation or during severe stress), and where AVHs are not very similar to those experienced by patients. Moving toward the other end of the continuum one may plot those individuals who have experienced AVHs from an early age, experience them relatively frequently, that are quite similar to those observed in patients with psychosis, are accompanied by subclinical levels of other symptoms (e.g., paranoid delusions, paranormal beliefs, formal thought disorder, depression, anxiety), and where there may also be a family history of psychiatric illness.

What these individuals all have in common with each other is that the experience of AVHs does not disturb their everyday life functioning—nor does the fact of having AVHs prompt them to seek professional help for these experiences. There is also a relatively good level of insight regarding these experiences and they do not fulfil criteria for a psychiatric or neurological disorder (nor have they ever had one in the past). However, at least two subgroups of non-patients along this continuum may be identified[1]. In one group, or non-patient type i, AVHs are not frequent and are not very similar to AVHs in patients. On the other hand, there are those, i.e., non-patient type ii, who experience AVHs very frequently and these are very similar to those experienced in patients. These two groups, moreover, probably plot somewhat differently on the above-mentioned continua. Regarding the continuum of experience, non-patients i plot toward the left, whereas

[1] Please note that there is most definitely overlap between these two subgroups, so they cannot be viewed as clearly distinct groups.

non-patients ii plot very close to the right. Similarly, turning to the continuum of risk, one may suggest that non-patients i plot to the left, whereas non-patients ii are situated to the right of the continuum. Also, this distinction will be important in the present article as studies in the literature have included non-patient groups of either type i or type ii. Important to underline here is that individuals of type i non-patients may include those based on vague and broad criteria mentioned earlier, and therefore AVHs experienced in this group of individuals are relatively far-removed from those experienced by patients. Moreover, as type ii non-patients experience AVHs that are closest to those experienced by psychotic patient groups, studies including these non-patient individuals will be emphasized as much as possible.

INCLUSION OF PATIENT VS. NON-PATIENT AVHs IN STUDIES

Studies that include non-patient groups in the context of AVHs have either (1) only included non-clinical participants or (2) have compared non-clinical and clinical participants in a direct manner, that is, in the same study with the same methodology. Both approaches have their merits, although it will be argued that the latter study design is the preferred of the two.

Studies including only non-clinical participants are interesting for a number of reasons. This study design allows one to avoid confounding effects (e.g., on cognitive test performance and neuroimaging data) associated with long-term medication and institutionalization, illness duration, low level of education, etc., present in patient populations. Also, studies that only include non-clinical persons provide an examination (and eventual validation) of the various components of the continuum hypothesis. These components may include, for example, distributional, phenomenological, developmental, and etiological components (Aleman and Larøi, 2008). The distributional component refers to the fact that AVHs should be present not only in subjects identified as "clinical cases" but also in a proportion of subjects from the general population that does not fulfil the clinical criteria of a patient. The phenomenological component consists of revealing a sufficient degree of inter-group similarity, in addition to a large degree of within-group variation, in terms of phenomenological characteristics of AVHs (e.g., degree of control, frequency, duration, emotional response, and content). The developmental component relates to aspects associated with the genesis of AVHs and that they should also be continuous between pathological and non-pathological samples. That is, factors identified as important demographic risk factors in clinical cases of hallucinations (e.g., younger age, higher level of urbanicity, lower income, lower level of education, unemployment, single marital status) should also be associated with the presence of hallucinations in non-clinical subjects. Finally, the etiological component maintains that clinical and non-clinical populations should share common ground in terms of underlying etiological mechanisms (e.g., cognitive, psychological, and neural mechanisms) of AVHs.

In contrast, comparing non-patient with patient AVHs in the same study has the vital advantage of being able to directly compare, as it were, these two "types" of AVHs. Moreover, and most importantly, such a study design is able to tease out both similarities and differences between these two groups. Where similarities are found, this points to mechanisms and factors that are not involved in the emergence of problematic AVHs. In contrast, where differences are found between these two groups, this indicates both possible factors and mechanisms involved in developing problematic AVHs, but also so-called "protective" mechanisms and factors that help prevent someone from developing problematic AVHs. Thus, including clinical and non-clinical individuals experiencing AVHs helps clarify which features of AVHs do not do necessarily reflect pathology (e.g., in cases where there are similarities between clinical and non-clinical groups) and, on the other hand, those features that may reflect pathology (e.g., in cases where the feature is present in clinical groups, but not in non-clinical groups). Such an approach clearly has clinical implications and will help identify new types of techniques to add to the ever growing arsenal of intervention strategies available for treating and managing hallucinations (cf. Larøi and Aleman, 2010).

What follows is a review of those studies that have done just that—compared clinical and non-clinical AVHs in the same study. Also, and for the reasons mentioned earlier, those studies including non-patients of type ii will be given priority. Moreover, these two types of AVHs will be compared in terms of their phenomenology, cerebral correlates, and cognitive mechanisms. Finally, emphasis will be made regarding eventual differences between patient and non-patient AVHs and thus another important characteristic of studies is that the study design allows for a clear demarcation of similarities and differences between groups.

PHENOMENOLOGICAL STUDIES

The term "phenomenology" may be used in a number of different ways. However, in this context it signifies the detailed description of the clinical and/or descriptive features of signs and symptoms observed in psychopathological conditions. In the case of AVHs, this refers to evaluating such characteristics as frequency, controllability, content, personification, emotional valence, duration, localization, loudness, and number of voices.

INCLUSION OF A NON-PATIENT GROUP

Although the phenomenological characteristics of AVHs in schizophrenia have been relatively well-described and studied in the scientific literature, this is clearly not the case with AVHs in non-patient populations. One exception is a recent and well-designed study by Sommer et al. (2010), whereby a group of non-clinical individuals experiencing AVHs is compared with a group of matched healthy subjects. One of the particular strengths of this study, and its study design, is the manner in which non-clinical individuals are carefully recruited, and this according to both strict and clear-cut criteria. A website providing information about hearing voices was created with various questions, including two items from the Launay–Slade Hallucinations Scale (LSHS, Larøi et al., 2004: "In the past I have had the experience of hearing a person's voice and then found that there was no-one there," "I have been troubled by hearing voices in my head"). Those with high scores on these two items were selected and were interviewed by telephone to confirm that they met the following criteria: (1) voices were distinct from thoughts and had a "hearing" quality, (2) voices were experienced at least once a month, (3) no diagnosis or treatment for psychiatric disorders other than

depressive or anxiety disorders in remission, (4) no alcohol or drug abuse for at least three months, (5) no chronic somatic disorder, (6) 18 years of age or older, and (7) four Dutch-born grandparents (to restrict heterogeneity for later genetic studies). This resulted in 103 individuals with AVHs and 60 control participants. Control participants scored 0 on both LSHS items, met the above-mentioned criteria, and were matched for sex, age, and education.

Characteristics of hallucinations were assessed with the Psychotic Symptom Rating Scales (PSYRATS; Haddock et al., 1999) and the LSHS. Results for the AVH group showed that the mean number of years experiencing AVHs was 29 years, and the mean age at first experiencing voices was 14 years. The types of voices experienced included commenting voices (18%) and voices speaking with each other (11%). The majority (71%) never heard AVHs with negative content only, 25% experienced both positive and negative AVHs, and 4% experienced AVHs with a negative content only. A great number (91%) reported no disturbance of daily life by their AVHs. AVHs were attributed to an external source in 58% of participants, mostly benevolent spirits. Based on structured clinical interviews, they did not have clinically relevant delusions, disorganization or negative or catatonic symptoms and did not meet criteria for cluster A personality disorder. Global level of functioning (Global Assessment of Functioning) was found to be lower than in the controls (82 and 87, respectively), although scores were within the normal range and lower levels was predominately attributable to lower levels of occupational functioning in the AVH group. There were significantly higher scores on the Schizotypal Personality Questionnaire (for both Total score and for scores on the Cognitive-perceptual, Disorganzational, and Interpersonal sub factors) and the Peters et al. Delusion Inventory (PDI), indicating a general increased schizotypal and delusional tendency in the AVH group. History of childhood trauma and family history of axis I disorders were also significantly more prevalent in these individuals compared to controls.

In summary, the AVH group experienced AVHs quite frequently and from an early age, but did not fulfil criteria for any clinical disorders. The AVHs they experience are both similar to those in (psychotic) patient groups (e.g., commenting voices, voices speaking with each other) but at the same time do not resemble those experienced by patients in that they very rarely have a negative content. The two groups did not differ considerably in terms of global social functioning, but did differ in terms of the presence of subclinical symptoms, history of childhood trauma, and family history of axis I disorders. According to the authors, these findings suggest that AVHs in otherwise healthy individuals is not an isolated phenomenon but, rather, part of a general vulnerability for schizophrenia. This might furthermore suggest a genetic predisposition for schizophrenia in the AVH group (e.g., based on a family history of axis I disorders), which, however, is also in interaction with various environmental risk factors (e.g., childhood trauma).

INCLUSION OF NON-PATIENT AND PATIENT GROUPS

As already mentioned, whilst studies only including non-patients participants, such as the above-mentioned study, provide us with important information concerning AVHs, the ideal study design is to compare AVHs in patient and non-patient populations. At present, only three studies (Leudar et al., 1997; Honig et al., 1999; Daalman et al., 2011) have compared AVHs in non-patients with patients suffering from psychosis.

The most recent study is Daalman et al. (2011). In this study, non-patient individuals were recruited in the same manner as described in Sommer et al. (2010). The non-patients ($n = 111$) did not meet criteria for DSM-IV diagnosis, whilst the patient group ($n = 118$) consisted of outpatients with a confirmed psychotic disorder. Both groups experienced AVHs at least once a month for over one year. The measure of AVHs included the PSYRATS (Haddock et al., 1999), in addition to five supplementary questions assessing aspects not included in the PSYRATS (e.g., age at onset, number of voices, personification, explanation of origin).

Results revealed higher scores for patients for the following AVH-related items of the PSYRATS: more negative content, higher distress and disruption of daily life, greater frequency, longer duration, and less controllability. Other phenomenological characteristics, such as perceived location of voices (heard inside or outside the head), loudness, number of voices, and personification (attribution to a real and familiar person), did not differ between the two groups. Interestingly, a very early mean onset of AVHs was observed in non-patients (12 years of age) and this was much lower than in patients (21 years). The beliefs that individuals held about the origin of hallucinations also differed. Non-patients frequently attributed their voices to spiritual sources (spirits of deceased people, guardian angels, entities, angels, presences), whereas patients often attributed their voices to real people, such as the secret police, telepathic people, drug gangs, or malevolent neighbors.

Previous studies of this kind have reported similar results. For instance, Honig et al. (1999) compared non-patients with two clinical groups (schizophrenia, dissociative disorders), all of whom were experiencing AVHs. The non-patient group was recruited via the local media, and included individuals with no previous psychiatric history, no recent onset of another psychiatric disorder and a score on the Dissociative Experiences Scale (Bernstein and Putnam, 1986) below 30. Hallucination assessment was carried out by means of a semi-structured interview with open-ended and closed questions relating to characteristics of the hallucinations (e.g., frequency, number, form, content, emotional qualities, gender, and age), history of the voices, circumstances related to the onset of hearing voices, present triggers, personal interpretation of the voices, coping strategies, and life history including traumatic experiences. Results revealed that non-patients generally felt in control of the experience, in contrast to the two patient groups. All three groups reported positive voices, but there were group differences in negative voices: these were reported by all in the schizophrenia group, 93% in the dissociative group, but only 53% in the non-patient group, suggesting that negative voices differentiated the groups. Moreover, the two patient groups were afraid of their voices, and reported significant disturbances in their daily life, and that the voices were critical and troublesome. A larger percentage of the non-clinical participants had an age of onset before 12 years of age (40%) compared

to the dissociative (33%) and schizophrenia (11%) groups. In terms of frequency, the daily and continuous experiences of voices were more frequent in the patient groups than in the non-patient group. Loci (AVHs experienced inside vs. outside the person) were similar in all three groups.

Finally, based on structured interviews, Leudar et al. (1997) examined specific pragmatic properties of AVHs (e.g., number of voices, characteristics that individuate the voices, sequential characteristics of the dialogs between voice hearers and their voices, dialogical positioning of voices hearers, voices and other individuals, and how the voices influence voice hearers' activities) and found no major differences in the structure and function of the AVHs of these two groups (non-patients and patients with schizophrenia both experiencing AVHs). However, they did note that patients with schizophrenia were more likely to identify their voices as being public figures, and that their voices were more likely to instigate violence. The voices of the non-patients were more likely to evaluate others, to have mundane content, and to be identified as being the voices of family members.

Thus, on a phenomenological level, there appear to be both similarities and differences between AVHs in patients and non-patients. Concerning similarities, this seems to be related to more perceptual and/or acoustic aspects such as such as localization, loudness, number of voices, and personification. Differences seem to be related to reactions to the voices and their effect on everyday functioning, in particular the negative emotional content of AVHs and the distress they elicit, in addition to higher frequency and less control. One other important difference is the age of onset of voices—around 12 years in non-patients compared to 21 in patients. As mentioned earlier, it is important to take into account, and better understand, these differences as they provide us with important clues as to why certain persons with these experiences are able to function normally in everyday life, whilst others (i.e., patients) are not.

NEUROIMAGING STUDIES

There has been an abundance of neuroimaging studies of AVHs in schizophrenia the past few years (cf. reviews and meta-analyses by Allen et al., 2008; Jardri et al., 2011; Kompus et al., 2011). In general, a distributed brain network has been shown to be implicated in the experience of AVHs. In their review of the literature, Allen et al. (2008) point to the involvement of secondary (and sometimes primary) sensory cortices, prefrontal, subcortical, and cerebellar regions. Recently, Jardri et al. (2011) performed a meta-analysis of studies ($n = 10$) examining cortical activation (fMRI, PET) during AVHs and found that they were associated with increased activity in fronto-temporal (especially those involved in speech generation and perception) and medial temporal (hippocampal/parahippocampal regions) areas. In a highly innovative recent study, Kompus et al. (2011) performed meta-analyses of neuroimaging studies (fMRI, PET) examining patients with schizophrenia (compared to healthy controls) during the processing of auditory stimuli (11 studies), and studies including patients experiencing AVHs in the absence of auditory stimuli (12 studies). The results revealed increased activation in the left primary auditory cortex and the right rostral prefrontal cortex when experiencing AVHs (and in the absence of an external stimulus) but, paradoxically, activation in these areas decreased in the presence of auditory stimulation in patients when compared with healthy controls. The authors suggest that this "paradox" is either caused by an attentional bias toward internally generated information and/or the failure of a default network to deactivate when auditory processing areas are engaged by external stimuli.

Although much research has been devoted to examining cerebral correlates in patients experiencing AVHs, only one study has compared patients and non-patients with AVHs (Diederen et al., in press). In this study, 21 non-psychotic subjects with AVHs and 21 matched patients with psychosis were asked to indicate the presence of AVHs during functional magnetic resonance imaging (fMRI). The non-patients were recruited in the same manner as described in Sommer et al. (2010). The patients with psychosis matched the non-patients for both demographic factors (e.g., age, sex, handedness) and for the total duration of AVHs, the mean duration of AVHs and the number of AVHs experienced during fMRI scans. Furthermore, for all participants, the AVHs had to be present with a frequency of at least four AVH episodes per scan, had to last at least 50 s, and participants had to clearly indicate both AVH onset and offset.

The results revealed that several areas were significantly activated during AVHs in both groups including the bilateral inferior frontal gyri, insula, superior temporal gyri, supramarginal gyri and postcentral gyri, left precental gyrus, inferior parietal lobule, superior temporal pole and right cerebellum. The activation of these areas during AVHs is in line with previous research including patients with psychosis with AVHs. Furthermore, and importantly, no significant differences in activation during AVHs between the groups were found. These findings suggest the involvement of the same brain areas in non-patient and patient groups during AVHs.

COGNITIVE STUDIES

There has also been much research examining the cognitive mechanisms involved in AVHs (cf. Aleman and Larøi, 2008). In general, there seems to be a consensus that AVHs occur when a private event is misattributed to a source that is external or alien to the self. A two-step process is most probably implicated in this (Larøi and Woodward, 2007) involving: (1) a form of autonoetic agnosia, or an inability to identify self-generated mental events and then (2) a misattribution, whereby these self-generated mental events are misattributed as coming from another (e.g., a non-self, external, alien) source. A number of cognitive mechanisms that might underlie this process have been identified in the literature and found to be associated with AVHs in patients with psychosis. These include inhibition, source memory, contextual memory, verbal self-monitoring, and metacognitive beliefs. A review of even a fragment of these studies is impossible in the context of this article and, therefore, the interested reader may refer to the many excellent reviews that exist on the topic (Seal et al., 2004; Ditman and Kuperberg, 2005; Nieznański, 2005; Aleman and Larøi, 2008).

What interests us most here, though, is whether these proposed cognitive mechanisms are also present in non-patient groups experiencing AVHs. However, although many studies have examined the role of these cognitive mechanisms in both patient

and non-patient groups, no study has done so in the same study[2]. Furthermore, only some form of non-patient type i have been included in these studies, unfortunately, leaving no study in the literature examining the role of cognitive mechanisms in type ii non-patients.

As an illustration, one proposed mechanisms involved in AVHs, verbal self-monitoring, will be described in general and in the context of studies of non-patients. One prominent model (Frith, 1987, 1992) maintains that AVHs are the result of defective self-monitoring, whereby defective monitoring of verbal thoughts leads to a failure in the recognition of one's own thoughts as self-generated and, as a consequence, these thoughts are misidentified as externally generated voices. A series of studies has tested this hypothesis using a verbal self-monitoring task. This task involves asking participants to pronounce a word, and then providing immediate auditory verbal feedback to participants via earphones. This verbal feedback may be: (1) the participant's own voice fed back to the participant, (2) another person's voice (albeit of the same gender) fed back to the participant, (3) the participant's own voice fed back to the participant but where the voice is distorted, or (4) another person's voice (of the same gender) fed back to the participant but where the voice is distorted. Participants are then asked to say if the verbal feedback is their own voice, someone else's voice or not sure. In general, results have found that patients with schizophrenia, and in particular those with AVHs, make more errors than controls, and moreover with a particular bias toward misattributing their own distorted voice to another person. Important to note is that the evidence that AVHs arise through a deficit in verbal self-monitoring alone is equivocal (Allen et al., 2007) as, for instance, this finding has not been found to be necessarily specific in patients with AVHs and many times is also associated with other symptoms, such as delusions.

Nevertheless, this line of research provides us with a good example, as this same task has also been tested in various forms of non-patient groups. In Johns et al. (2010), persons with At Risk Mental State (ARMS) were compared with a group of healthy controls on this task. The former group consisted of individuals who experience attenuated forms of psychotic symptoms—symptoms that are similar to full psychotic symptoms but less severe and associated with greater insight. Results revealed impaired verbal self-monitoring in the ARMS group compared to controls (i.e., greater number of errors when own speech was distorted and more likely to misattribute distorted own speech to another source). Furthermore, the authors mention that the verbal self-monitoring deficit seemed "to be less marked than in patients with schizophrenia" although this could not be directly tested due to the fact that a group of psychotic patients was not included in the study. Allen et al. (2006) used a similar task, albeit in a group of healthy individuals (University undergraduates) who completed scales measuring proneness toward hallucinations (LSHS) and delusions (PDI, Peters et al., 1999). Results showed that misattribution errors on the verbal self-monitoring task for own distorted speech was significantly correlated to scores on the PDI but that there was only a trend for a correlation with scores on the LSHS. Finally, Versmissen et al. (2007) compared patients with psychosis, and subjects from the general population with a high level of psychotic experiences, on the verbal self-monitoring task. The authors did not report significant differences between the groups and, furthermore, mention that there were no abnormal performances on the task.

Thus, in terms of cognitive studies—even amidst the multitude of possible cognitive mechanisms implicated in AVHs based on research with psychotic patients, studies have tested these mechanisms in non-patient groups alone—but no study to date has included both patient and non-patient groups. Furthermore, at present, no study has included the all-important non-patient type ii group. This results in it being highly difficult to suggest which cognitive mechanisms are present in non-patient AVHs, and impossible to say anything about which mechanisms are involved (or not) in non-patient compared to patient AVHs. Verbal self-monitoring studies were used to illustrate this.

CONCLUSIONS

In general, some studies have managed to tease out both similarities and differences in patient and non-patient AVHs. The greatest progress, however, is probably on a phenomenological level. Here, it seems that differences between patients and non-patients regards the reactions to AVHs and the effect AVHs have on everyday life functioning. In contrast, in terms of cerebral areas involved in patient vs. non-patient AVHs, there are far too few studies examining this issue. The only existing study of this kind did not observe any significant differences between cerebral activation in patient and non-patient AVHs. This finding is interesting in itself, but evidently needs to be replicated in future studies. Regarding cognitive mechanisms, unfortunately, there are no studies that have directly compared clinical and non-clinical AVHs and, therefore, it is difficult to determine whether or not cognitive mechanisms (inhibition, source memory, verbal self-monitoring, meta-cognitive beliefs) found to be present in patient groups also play a role in AVHs in non-patient groups. Studies that have included non-clinical participants (type ii) suggest that the same cognitive mechanisms found to be involved in AVHs in patients are also involved in non-patients. Whether they are to the same extent as in patient groups, or whether deficit levels are observed in these non-patient AVHs, however, is not known and needs to be examined in future studies.

On a more general note, and as mentioned by Badcock and Hugdahl (2012), there is a grave need for future studies to more directly examine similarities and differences of patient and non-patient AVHs on phenomenological, cognitive, cerebral (and other) levels by including both types of individuals. It was mentioned that those non-patient studies examining, for instance, cognitive mechanisms suggest that these same mechanisms are implicated in both patient and non-patient AVHs. However, as this has yet to be directly examined in studies, this can only be characterized as being a tentative interpretation. Indeed, it is possible that certain cognitive mechanisms are only implicated in patient AVHs, yet to date studies have not been designed to test this important hypothesis in a direct manner. We have

[2]Kindly note that Badcock and Hugdahl (2012) have provided an excellent review and discussion of possible patterns of shared and distinct cognitive (and neural) AVH mechanisms in clinical and non-clinical populations.

perhaps (unknowingly) been too intent on identifying similarities between patient and non-patient AVHs and at the same time have not fully realized the significance of detecting differences between these two. Consequently, future studies will also need to ensure that study design will allow a clear demarcation of similarities and differences between groups. Finally, the approach adopted by Sommer and colleagues regarding recruitment of non-patient individuals with AVHs is the best method as it allows for the identification of non-patients of type ii, which are very close on a number of levels to those AVHs experienced by patients with psychosis. Hopefully other researchers will adopt a similar recruitment method in forthcoming studies.

As a result of recent phenomenological studies, and in particular Daalman et al. (2011), two major differences seem to stand out when comparing patient and non-patient AVHs, and therefore, merit further discussion: (1) the negative emotional content of AVHs in patients and the distress they elicit, the higher frequency, and less controllability, and (2) the lower age of onset of AVHs in non-patients (12 years) compared to patients (21 years). Negative content might explain both higher levels of distress and frequency, and less control. That is, experiencing AVHs with a highly negative content will render these experiences distressful for individuals, leading to increased frequency and consequently to less controllability due to a number of processes such as a rebound effect. What remains to be explained is why patients' AHVs are so negative. Studies have shown that childhood trauma is present in non-patients experiencing AVHs (cf. Sommer et al., 2010) and a growing body of research has similarly revealed that patients with psychosis with AVHs have experienced early trauma (cf. Fowler et al., 2006)[3]. Moreover, certain authors have convincingly argued that AVHs should be considered as a dissociative experience and, in particular, as an after-effect of traumatic or highly stressful experiences (cf. Moskowitz and Corstens, 2007). This might also contribute to an understanding as to why non-patient individuals who experience AVHs have such an early onset (12 years of age), that is, in a period where such traumatic experiences may have occurred. Escher et al. (2004) report that in their cohort of 80 children and adolescents who experienced AVHs, in about 75% of them, the onset of AVHs was related to traumatic events or circumstances beyond their control (e.g., death of someone close, problems in the home situation or school, sexual abuse, long-term physical illness, etc.). Another key to trying to understand these findings may be related to emotion regulation strategies. A study (van der Meer et al., 2009) using the Emotion Regulation Questionnaire (ERQ; Gross and John, 2003) has shown that patients with psychosis, compared to healthy controls, tend to use suppression more often and reappraisal strategies less often[4]. This pattern in relation to symptomatology was not examined in this study, however, a recent study (Badcock et al., 2011), also using the ERQ, found that, within their group of patients with schizophrenia, an increased use of suppression correlated positively with AVH severity (frequency, duration, loudness). Thus, non-patients, in face of traumatic and/or highly stressful situations develop AVHs as a dissociative reaction to these events but thanks to the increased use of adaptive (e.g., reappraisal) and the decreased use of maladaptive emotion regulation strategies (e.g., suppression), these individuals are able to adequately cope with the emotional force of these experiences and, therefore, they will not have a major influence on the content of the AVHs in these persons. In contrast, it may be proposed that patients with psychosis who experience AVHs who are also confronted with highly stressful or traumatic events resulting in dissociative experiences such as AVHs, and that due to the use of maladaptive emotion regulation strategies (and the absence or less frequent use of more adaptive strategies)—these individuals are not able to appropriately cope with the emotional intensity of these experiences resulting in these experiences having a profound influence on the content of their AVHs. Indeed, the use of maladaptive emotion regulation strategies, such as suppression, is related to a number of non-beneficial consequences such as an inability to reduce the experience of unwanted emotions. The precise mechanisms and processes involved in this (i.e., the dissemination of these strong emotions into the contents of AVHs), however, are not known and, therefore, need to be directly examined in future studies. Unfortunately, though, no study has directly examined patients compared to non-patients with AVHs regarding their use of emotional regulation strategies. However, and as mentioned earlier, in order for future studies to maximize possibilities of identifying similarities—but most important differences—between patient and non-patient groups with AVHs (and furthermore due to the complex and multi-dimensional nature of emotional regulation itself), it will probably be best to include an extensive and multi-dimensional battery of emotion regulation measures such as the Cognitive Emotion Regulation Questionnaire (Garnefski et al., 2001) that includes a number of adaptive (e.g., acceptance, positive refocusing, refocus on planning, positive reappraisal, putting into perspective) and maladaptive (e.g., self-blame, rumination, catastrophizing, blaming others) strategies, and not just the ERQ, which evaluates only suppression and reappraisal. Furthermore, in order to properly test this hypothesis, such investigations would have to take place early in the individuals' lives, such as in childhood. Another issue that needs to be addressed is why patients develop their AVHs much later (i.e., late adolescence/early adulthood) and not in childhood when the majority of these traumatic events are likely to occur.

Finally, a number of other issues also need to be examined in future studies. It was mentioned that combined epidemiological and longitudinal studies have shown that the transition from a non-clinical AVH to a clinical AVH is related to appraisals of these experiences and how people cope with them. Concerning the latter point, research presented in the present article suggests that it may also be important to examine how people cope with emotions in general (via emotion regulation strategies) and not just how they cope with the AVHs themselves. Regarding the former point, studies (cf. Birchwood and Chadwick, 1997) show that much emotional (e.g., distress depression, anxiety) and voice-driven behavior (e.g., maladaptive coping strategies) in patients experiencing AVHs is mediated by the beliefs they

[3]As this has not yet been done, it would be interesting for future studies to directly compare patient and non-patient groups experiencing AVHs in terms of early traumatic experiences (e.g., timing, frequency, type of events, etc.).

[4]Kindly note, however, that some studies have not replicated this finding (cf. Henry et al., 2007, 2008).

have about the voice's identify (e.g., a malevolent, omnipotent, or omnipresent voice). For instance, voices believed to be malevolent provoke fear and anger and are resisted, whereas benevolent voices are associated with positive affect. It would be interesting to examine the types of beliefs that non-patients have regarding their voices. In this context, it is likely that non-patients do not frequently hold beliefs that their voices are malevolent and omnipotent, as Daalman et al. (2011) showed that non-patients often attribute their voices to (benevolent) spiritual sources (such as spirits of deceased people, guardian angels, entities, angels, and presences) and furthermore that AVHs in non-patients rarely provoke negative emotions such as distress and are rarely negative in content. Nevertheless, an examination of this issue merits to be carried out. Similarly, it would be noteworthy to examine if changes (described earlier in the article) in mental experiences—such as changes in the stream of thought—occurring before AVHs develop during prodromal phases in patients, also occur in non-patients.

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Patients with schizophrenia fail to up-regulate task-positive and down-regulate task-negative brain networks: an fMRI study using an ICA analysis approach

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Recent research suggests that the cerebral correlates of cognitive deficits in schizophrenia are nested in the activity of widespread, inter-regional networks rather than being restricted to any specific brain location. One of the networks that have received focus lately is the default mode network. Parts of this network have been reported as hyper-activated in schizophrenia patients (SZ) during rest and during task performance compared to healthy controls (HC), although other parts have been found to be hypo-activated. In contrast to this network, task-positive networks have been reported as hypo-activated compared in SZ during task performance. However, the results are mixed, with, e.g., the dorsolateral prefrontal cortex showing both hyper- and hypo-activation in SZ. In this study we were interested in signal increase and decrease differences between a group of SZ and HC in cortical networks, assuming that the regulatory dynamics of alternating task-positive and task-negative neuronal processes are aberrant in SZ. We compared 31 SZ to age- and gender-matched HC, and used fMRI and independent component analysis (ICA) in order to identify relevant networks. We selected the independent components (ICs) with the largest signal intensity increases (STG, insula, supplementary motor cortex, anterior cingulate cortex, and MTG) and decreases (fusiform gyri, occipital lobe, PFC, cingulate, precuneus, and angular gyrus) in response to a dichotic auditory cognitive task. These ICs were then tested for group differences. Our findings showed deficient up-regulation of the executive network and a corresponding deficit in the down-regulation of the anterior default mode, or effort network during task performance in SZ when compared with HC. These findings may indicate a deficit in the dynamics of alternating task-dependent and task-independent neuronal processes in SZ. The results may cast new light on the mechanisms underlying cognitive deficits in schizophrenia, and may be of relevance for diagnostics and new treatments.

Keywords: schizophrenia, fMRI, ICA, cognitive processing, default mode network, executive network, brain activation, dichotic listening

INTRODUCTION

There is a considerably body of evidence showing that patients with schizophrenia reveal global cognitive deficits (see, e.g., Gold and Harvey, 1993; Egeland et al., 2003; Rund et al., 2006) in a range from low-level perceptual processes to high-level attention and executive processes (see Green et al., 2000; Green et al., 2004). A comparable body of both ERP and functional neuroimaging studies has likewise revealed corresponding changes in activations in specific brain areas related to specific cognitive processes (Callicott et al., 1998; Hugdahl et al., 2004; Pearlson and Calhoun, 2009 for data and selective reviews; Agarwal et al., 2010; Brown and Thompson, 2010; Gur and Gur, 2010; Dias et al., 2011). The current literature is however ambiguous regarding the exact nature of activation localization and the magnitude and direction of activation differences between patients and healthy controls (HC), with both hypo- and hyper-activations being reported in the patients (Callicott et al., 2003; Egan et al., 2004; Hugdahl et al., 2004; Rasser et al., 2005; Weiss et al., 2007). An explanation for this diversity regarding the imaging studies may be that the neuronal correlates of global cognitive deficits most likely involve large-scale networks that would be common for a variety of cognitive processes, and go beyond solitary activations (c.f. Smith et al.,

2009). Complicating factors are however, the diversity of the tasks being performed while the subject is in the MRI scanner, and the small number of participants often used in imaging studies (see for example review Adams and David, 2007). Another factor may be the general disorganization of cortical networks in schizophrenia (Bassett et al., 2008) and the existence of different connectivity patterns among brain regions in schizophrenia compared to HCs (Jafri et al., 2008). Thus, both hyper- and hypoactivation may be present simultaneously if up-regulating (higher signal intensity) of one network will require the down-regulation (lower signal intensity) of another network (c.f. Hugdahl et al., 2009a) in order for efficient cognitive processing to occur. This was also recently suggested by Guerrero-Pedraza et al. (2011), who found that the co-existence of frontal hypo- and hyperactivation could be mediated by aberrant network dynamics with regard to up- and down-regulation of cortical networks. It is therefore appropriate at the systems level of explanation (Friston et al., 1999; Wright et al., 1999) to approach a global cognitive failure in schizophrenia with a large-scale multivariate analysis approach.

Recent imaging studies have shown differences between schizophrenia and control subjects in intrinsic connectivity networks, mostly during resting state periods with no explicit cognitive task to be performed (Calhoun et al., 2008, 2009; Rotarska-Jagiela et al., 2010), in particular indicating differences in the default mode network (Raichle et al., 2001; Garrity et al., 2007; Raichle, 2010). In another study where the auditory oddball task was performed, Kim et al. (2009b) discussed the possibility that patients suffering of schizophrenia might have difficulties shifting from baseline network activity to networks involved in task performance.

We therefore compared signal decreasing and signal increasing during alternating task-present and task-absent epochs while the participants were in the scanner. A possible disturbance in the patient group, would potentially interfere with the ability to adequately monitor, process, and evaluate stimuli in the surrounding environment, in short, would interfere with cognitive processing. In order to drive task-positive and task-negative networks that would correspond to a global cognitive deficit, one will need a corresponding "global" cognitive task that encompasses cognitive processes at different levels of processing demands. We have previously used a modified dichotic listening (DL) task with simple speech sounds and with instructions to focus attention on either the left or right ear stimulus (Hugdahl and Andersson, 1986; Løberg et al., 1999; Hugdahl et al., 2009a). This task has shown to encompass three different cognitive components in the same experimental design, with maximum experimental control of extraneous confounding factors. The three processes are a basic auditory perception component, an attention focus component, and an executive control component (c.f. Hugdahl et al., 2009b for further details; Bouma and Gootjes, 2011), going from low-level to high-level processing demands. A unique feature of the instruction-modulated DL task is that the stimuli and general procedure stay the same across all three instructions, with minimalistic experimental manipulations between conditions. When also analyzing data by combining data from all three conditions into a common measure we obtain an estimate of the overall cognitive processing. This would include both basic sensory and complex cognitive processes embedded within the same experimental frame. Such an approach will also be less sensitive to shifts of processing modes between tasks as is typical of standard neuropsychological tests, which also differ in overall task difficulty and task design and outline.

In order to investigate the different networks involved in the alternating task-dependent and task-independent neuronal processes during alternating epochs of task presence and absence, we used an independent component analysis (ICA) approach when analyzing the fMRI data. ICA is a model-free way of analyzing fMRI data by extracting the different time-courses attached to voxel-wise spatial locations (Calhoun et al., 2001, 2009). By identifying voxels showing signal increasing during time-courses that correspond to task-positive (task presence, or positive difference measure ON-OFF blocks) versus voxels showing signal increasing during time-courses corresponding to task-negative (task absence, or negative difference measure ON-OFF blocks) time-series, and comparing these signal intensities between groups, it would be possible to simultaneously identify corresponding anti-correlated signal increasing and signal decreasing differences between the groups. We further assumed that mean average difference between task ON and OFF conditions is an informative feature of the dynamics of alternating task-positive and task-negative neuronal processes. Regarding task-positive and task-negative networks, we would like to point out that different studies have reported mixed results regarding task-positive and task-negative networks in patients and HCs (see for example Garrity et al., 2007; Kim et al., 2009a; Mannell et al., 2010). However we specifically predicted that patients should be deficient compared to controls in up-regulation of the executive network (labelled effort network by Hugdahl et al., 2009a), showing reduced signal intensity in the included ICA components, and also be deficient in down-regulation of selected components included in the default mode network (see Sridharan et al., 2008). Further, we predicted that the anterior cingulate cortex (ACC) would be particularly activated in the patient group when switching between network operational modus, based on the findings on healthy individuals reported by Sridharan et al. (2008), where this area together with the right fronto-insular cortex seems to act to switch between the two networks.

MATERIALS AND METHODS

PARTICIPANTS

The present study included 31 patients diagnosed with schizophrenia (SZ, 22 male/eight female, all-right-handed, Age; mean = 35, range 18–57, SD = 10.24, median = 37, Years of education: mean = 13, range 9–19, SD = 2.72, median = 13) and 31 HC (22 male/eight female, four ambidextrous hand preference/27 right-handed, Age; mean = 35, range 19–59, SD = 10.30, median = 39, Years of education: mean = 15, range 10–24, SD = 2.96, median = 15). All participants gave written informed consent and the study was approved by the Regional Ethic Committee for Medical Research. The SZ and HC groups were matched for age, gender, and years of education on a one-to-one basis (see **Table 1**). The SZ had previously been diagnosed according to both the Diagnostic and Statistical Manual of Mental Disorders Revised

Table 1 | Demographics regarding the participants in the study: due to missing data the * indicates that the average was used.

Age_SZ	Age_HC	Sex	Education_SZ	Education_HC	Duration of illness_SZ	Age at onset_SZ	Equivalent dosage_SZ
30	29	1	12	17	6	24	2.5
24	23	1	9	16	7	17	0.0
29	28	1	12	17	9	20	1.5
37	36	1	15	16	5.5	32.5	2.0
43	39	2	16	13	4.5	38.5	1.0
34	32	1	14	24	5	29	0.6
35	33	2	16	12	8	27	0.7
34	33	1	13	14	8	26	2*
34	36	1	18	12	6	28	0.0
37	37	1	19	15	5	32	0.5
33	31	1	17	17	6.5	26.5	2.2
55	57	1	10	10	32	23	2*
26	24	1	12	11	8	18	1.0
26	27	1	9	14	6.5	19.5	0.8
25	26	2	12	18	6	19	2*
18	22	1	12	14	13*	22*	5.0
37	39	1	15	15	13*	22*	0.5
42	40	1	13	13	21	21	0.8
44	42	1	10	15	25	19	0.8
41	40	1	9	19	34	7	5.0
38	39	2	17	15	16	22	2.5
57	59	1	12	14	33	24	1.8
43	40	1	12	17	8	34	2.5
27	27	2	12	19	19	8	4.5
20	19	2	14	12	13	7	4.2
49	51	1	15	16	22	27	0.8
19	19	2	11	11	2	17	0.8
40	39	1	13*	18	13*	22*	2*
46	45	1	12	16	27	19	6.6
19	19	2	11	13	4	15	0.0
43	42	1	13*	12	13*	22*	2*

The mean age for the patients was as for the healthy controls 35 years. The patients had on average 13 years of education while the healthy controls had 15 years. Females are given the number 2 while males are numbered 1 under the sex label.

Fourth Edition (DSM-IV) and the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Equivalent drug dosage for all drugs used was calculated among the SZ by conversion to defined daily doses (DDDs) as developed by the World Health Organization Collaborating Center for Drug Statistics Methodology[1]. The basic definition of the DDD unit is the assumed average maintenance dose per day for a drug used for its main indication in adults. Three SZ were not using any medication at the time of scanning, and information from four SZ was not available. These four SZ were included with imputations of the average dose based upon the group average (see **Table 1** for further information). The SZ group underwent the Positive and Negative Syndrome Scale (PANSS) interview (Kay et al., 1987) about 30 min before MR-scanning.

Handedness was established by the handedness-questionnaire first suggested by Raczkowski et al. (1974). The participants were considered right-handers if they used the right hand (one foot item) in least 13 of the 15-items in the questionnaire.

Exclusion criteria were left-handedness, a hearing deficit of more than 20 dB on any of the frequencies 500, 1000, 2000, and 4000 Hz or an interaural difference larger than 15 dB. Hearing was tested with the Oscilla® AudioConsole software program[2], or manually by use of Micromate 304 Audiogram[3]. Among the HC there was no history of drug abuse or psychiatric illness. All participants were paid compensation (500 NOK, ∼90 USD) for their expenses and use of time.

THE COGNITIVE TASK

We used a DL paradigm with six consonant-vowel (CV) syllables, ba/ta/ga/pa/ka/da, that were presented dichotically, i.e., two different syllables simultaneously, one in each ear. The subjects

[1]http://www.whocc.no

[2]http://www.inmedico.com

[3]http://www.otometrics.com

were in addition instructed to focus attention to and report from either the left (forced-left attention, FL) or right ear (forced-right attention, FR) stimulus, or with no instruction of attention focus (non-forced focus, NF). Previous studies (Hugdahl et al., 2009b) have shown that the NF condition taps a lateralized perceptual component, the FR condition taps a non-executive attention component, and the FL condition taps an executive cognitive control component. There were a total of 30 syllable-pair representations. The participants were not informed about the dichotic nature of the task, and were only told that they would be hearing series of syllable sounds that would come about every fourth second, and that they should orally report after each presentation which syllable they heard best or first. Oral responses were transmitted via an in-house built air-conducting microphone that was placed on the head-coil and subsequently recorded on a digital recorder (M-audio Microtracker 24/96[4]) outside the scanner room. Responses were later scored, by use of GoldWave audio software version 5.55[5]. On the MR examination day instructions about the DL task and what was expected of the participant were given orally before the experiment began and again in written form via LCD goggles (NordicNeuroLab[6]) during scanning. The instruction to report the right or left ear stimulus during the FR and FL attention conditions, respectively, was indicated by an arrow in the goggles together with written instructions, also presented in the LCD goggles.

MR IMAGING

The MR-scanning was done with a 3.0 Signa HDx MR scanner. Anatomical images were recorded with a high-resolution T1-weighted sequence for 3D volume images before the functional scans were acquired with an echo planar imaging (EPI) sequence. The T1-images were acquired with an EPI sequence. The T1-images were acquired with a FSPGR pulse sequence with 122 sagittal slices [64×64 matrix size, slice thickness $= 1.0$ mm, echo time (TE) $= 30$ ms, repetition time (TR) $= 1.5$ s, flip angle (FA) $= 90$].

The T1-weighted 3D volume images were used for positioning of the slices for the definition and identification the functional EPI volumes parallel to the AC-PC line. A sparse-sampling EPI sequence protocol was used with a silent "gap" between successive volume acquisitions when the auditory stimuli were presented and the verbal responses collected (van den Noort et al., 2008; van Wageningen et al., 2009). The sparse-sampling protocol had the following parameters: TA $= 1.5$ s, TR $= 5.5$ s, voxel size $= 3.44$ mm $\times$ 3.44 mm $\times$ 5.5 mm, volumes acquired $= 184$, slice thickness $= 3$ mm, FA $= 90$. Four "dummy" scans were acquired at the beginning in order to avoid confounding by initial arousal and other effects.

The CV-syllables presentation started 0.6 s after the TA, leaving approximately 2.9 s for the oral response recording after each stimulus presentation.

fMRI DATA PRE-PROCESSING AND STATISTICAL ANALYSIS

The DICOM images were converted to the ANALYZE file format using the nICE software version 2.3.6[7] The images were preprocessed using the Statistical Parametric Mapping (SPM8) software package (Wellcome Trust Centre for Neuroimaging[8]) implemented in Matlab R2009b (Mathworks Sherborn, MA, USA[9]). Images where further realigned and corrected for possible movement distortion (unwarp) and normalized into the Montreal Neurologic Institute (MNI) reference brain space (Ashburner and Friston, 1999), where the EPI template included in the SPM8 software was used. The normalized images were then resliced with a voxel size of 3 mm^3 and smoothed using an 8-mm full-width at half maximum of the Gaussian smoothing kernel.

Group-level spatial ICA was then performed (Calhoun et al., 2001) with the GIFT toolbox, version 1.3h[10] implemented in Matlab, with a two-step principal component data reduction, Infomax ICA (Bell and Sejnowski, 1995) with ICASSO (Himberg et al., 2004) and subsequent back-reconstruction. In the first reduction step, the data were intensity-normalized, scaling voxel time-series to a mean of 100, before the data were reduced with temporal principal components analysis (PCA) within subjects. This data reduction step privileges differences among the subjects (Erhardt et al., 2011). Hence the dimensionality of the data was reduced from 180 time points to 90 principal components.

In a second data reduction step, the individual components were concatenated across subjects and further reduced to 60 components. Infomax ICA was performed in this aggregate dataset, estimating the 60 components. The ICA was performed 100 times with random initial conditions, hereafter using ICASSO (Himberg et al., 2004) to assess the stability of the components and using the centroids for back-reconstruction of individual components. For reconstructing subject specific images and enable comparison of both time-courses and spatial maps for both the groups, the "GICA3" back-reconstruction method was used (recommended also by Erhardt et al., 2011).

Prior to the group-level analysis, we selected task-dependent components by means of a simple amplitude criterion. The reconstructed time-series of each participant's components set were filtered with a Butterworth 256s hi-pass filter and then segmented into four ON-OFF blocks repeats and averaged. The distribution of the component amplitudes was then assessed, i.e., sorted on the overall amplitude differences and six components (three from each tail) were selected for further testing, i.e., 5% largest signal increases (task-positive) and 5% largest signal decreases (task-negative), respectively to the DL task across the whole sample. These independent components (ICs) were then tested for significant group differences. In order to control for covariates of no interest, we used a multiple linear regression model with sex, age, and the years of education as predictors and tested for group differences in the residual. Due to scanner upgrade during the data

[4]http://www.m-audio.com or a DAT recorder
[5]http://www.goldwave.com
[6]http://www.nordicneurolab.no
[7]http://www.nordicneurolab.com
[8]http://www.fil.ion.ucl.ac.uk
[9]http://www.mathworks.com
[10]http://icatb.sourceforget.net

acquisition period, we had to rectify the intensity signal differences. Regarding these signal differences, the mean image intensity changed and the directionality of the effects remained constant. This has been taken into consideration and is calculated for as a covariate in these analyses.

The difference in signal intensity between the two groups was further evaluated for the six components showing the largest absolute difference between the ON-OFF epochs. We assumed reduced signal intensity in the SZ, and used a Mann-Whitney U-test due to non-parametric distribution of the residuals within each group with a one-tailed significance level at $p <= 0.05$ (see also **Figure 1** for further information and results).

RESULTS

BEHAVIORAL DATA

There was a significant difference between the groups in overall performance on the DL task (pairwise two-sided t-test: $p = 0.042$), with the HC group showing higher accuracy for reported syllables. For further details regarding behavioral data, see **Table 2**.

fMRI DATA

Back-reconstructed individual component maps were subjected to voxel-wise mass-univariate one-sample t-test implemented in the SPM8 software. Component activations were considered significant at $p < 0.01$ FWE. The regional activation maxima are reported below and illustrated in **Figure 1** (see also **Table 3** for further details regarding the activation maxima in the ICs). The following networks were identified.

IC1-AUD1

An auditory network with signal intensity detected bilateral in the superior temporal gyri, with slight leftward dominance (−42, −25, 10, $t = 36.09$).

Table 2 | Behavior data score shown as percentage (significant group difference; $t = 0.42$).

	NFR%	NFL%	FRR%	FRL%	FLR%	FLL%
Mean percent score_HC	45.16	30.00	61.11	21.22	42.47	38.39
Mean percent score_SZ	39.78	31.29	46.02	29.68	38.28	34.30
Max_HC	76.67	76.67	86.67	43.33	83.33	86.67
Max_SZ	70.00	56.67	76.67	50.00	66.67	66.67
Median_HC	40.00	30.00	46.67	30.00	40.00	33.33
Median_SZ	50.00	26.67	65.00	23.33	40.00	33.33
Min_HC	13.33	6.67	26.67	6.67	6.67	6.67
Min_SZ	13.33	10.00	16.67	10.00	13.33	13.33
Stdav_HC	15.51	15.56	15.64	10.26	17.99	19.13
Stdav_SZ	15.10	12.07	13.70	11.33	12.56	11.96

NF stands for "non-forced" task instruction, FR stands for "forced-right" task instruction, and FL stands for "forced-left" task instruction. The last letter indicates whether the percentage score is from the right ear (R) or left ear (L) respectively.

IC2-EXE

An executive network with bilateral signal intensity detected in the Insula, with leftward dominance (−42, 14, −5, $t = 30.81$) together with signal intensity detected in supplementary motor cortex (SMA). The SMA signal intensities also showed a leftward dominance (−3, 8, 49, $t = 17.72$). The dorsolateral area of the ACC also showed signal intensities in the IC2-EXE component (−6, 23, 31, $t = 9.01$). The IC2-EXE component is typically involved in cognitive control/performance monitoring network component (see for example Cole et al., 2010).

IC3-AUD2

A second auditory network with bilateral signal intensity in the inferior and middle temporal gyri with leftward predominance (−54, −31, −14, $t = 25.40$ and −63, −25, −14, $t = 21.29$, respectively).

IC4-VIS

A visual network with bilateral signal decreasing with predominance to the right in the fusiform gyri (30, −61, −17, $t = 31.88$), the cerebellum (30, −52, −23, $t = 24.87$), and the occipital lobe (42, −82, −5, $t = 19.24$).

IC5-aDMN

An anterior default mode network with bilateral signal decreasing in the ventromedial prefrontal cortex/anterior cingulate with rightward predominance (12, 38, 1, $t = 39.06$).

IC6-pDMN

A posterior default mode network with bilateral signal decreasing in the precuneus with leftward predominance (−3, −55, 31, $t = 44.57$) and rightward preponderance for the angular gyrus (51, −64, 31, $t = 18.30$).

Three out of the six selected components showed significant ON-OFF difference between the groups. IC2-EXE showed significantly less signal intensity in the SZ group ($p = 0.04$). Significant lesser signal decreasing in the SZ group was seen in IC4-VIS ($p = 0.001$) and IC5-aDMN ($p = 0.003$; see **Table 4** for further information for group differences across components). Regarding spatial differences among the component maps, no differences were detected with a two sample t-test, indicating that the overall topography of the networks did not change while alternating between ON (task presence) and OFF (task absence) periods, while the signal intensity did.

POSITIVE AND NEGATIVE SYNDROME SCALE

There were two significant correlations between IC components and PANSS symptoms. These correlations were however driven by anomalies in the distributions, and we therefore conclude that the ICs and PANSS symptoms in essence were non-correlated (see **Table 5**; **Figure 2** for details).

DISCUSSION

Focusing on the 10% of ICA components with the highest BOLD-fMRI signal amplitudes revealed significant differences between the two groups in three of the component networks. One component related to task-positive networks: the IC2-EXE showed

reduced signal intensity in the SZ group in the Insula, SMA, and dorsolateral section of the ACC. The IC4-VIS showed increased signal intensity in the SZ group in the fusiform gyri, in the anterior lobe, and in the occipital lobe. The IC5-aDMN showed increased signal intensity in the SZ group in the ACC. Taken together, these findings indicate impaired signal decreasing in the SZ group compared to the HC group of components belonging to task-negative, or absence, networks during OFF epochs, and a corresponding failure of up-regulating components belonging to task-positive, or presence, networks during ON epochs.

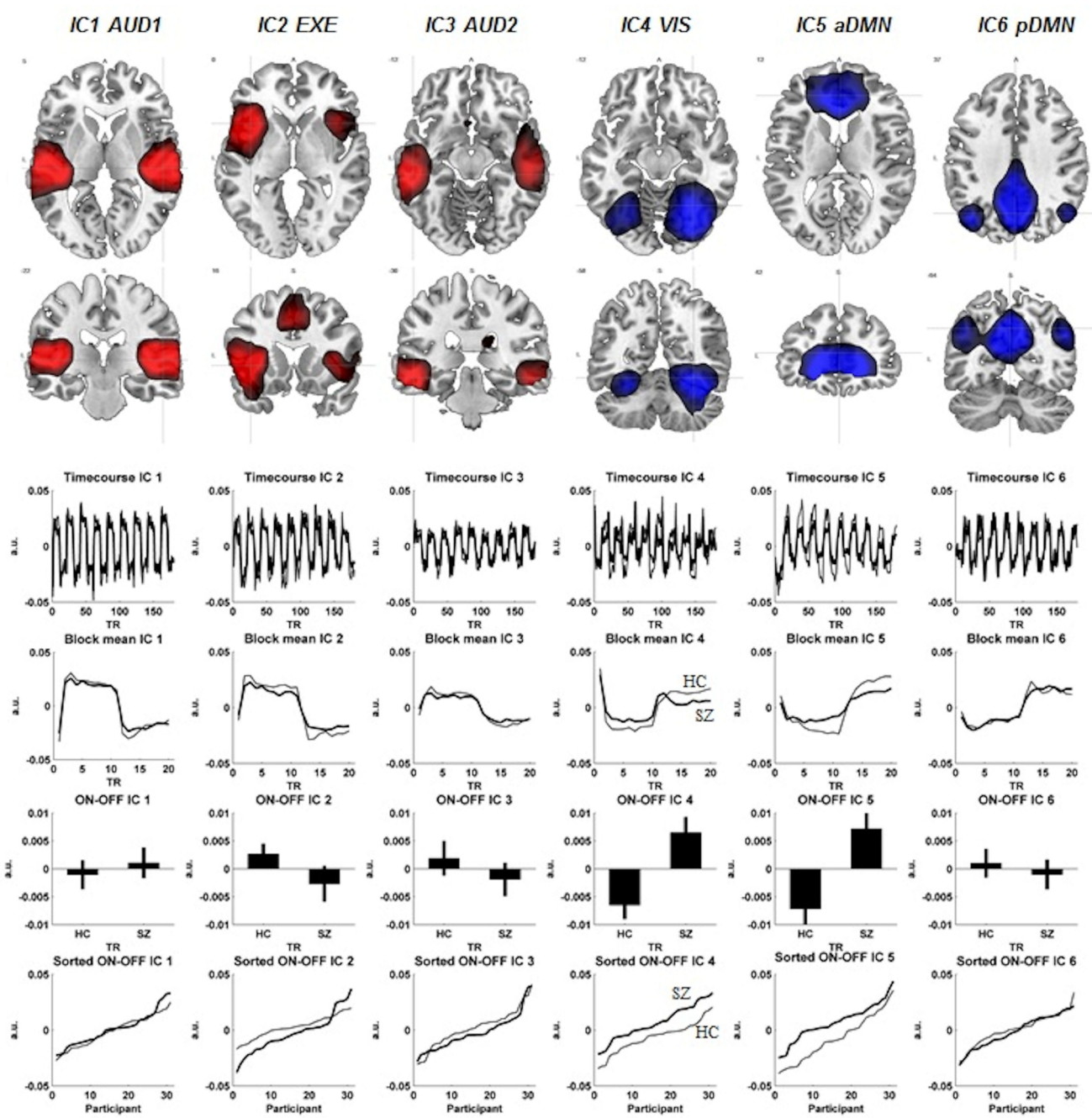

FIGURE 1 | The figure displays each components spatial extension (FWE correction, $p < 0.01$, cluster extension of 10 voxels). Below each component are corresponding time-courses, the ON-OFF block difference expressed as positive signal change, co-registration effects shown as standard error of the mean in both groups and last the ON-OFF block activation difference visualized between the two groups. The schizophrenia patients (SZ) are visualized with the thicker black line, whereas the healthy controls (HC) have the thinner black line in the figure. The red color represents the activation situation (ON), whereas the blue color visualizes the de-activation (OFF).

Table 3 | The ICs MNI coordinates and respective degree of activation in clusters defined.

IC	Set-level		Cluster-level			Voxel-level					*x*	*y*	*z*
	p	*c*	$p_{corrected}$	k_E	$p_{uncorrected}$	$p_{FWE-corr}$	$p_{FDR-corr}$	*T*	(*z*)	$p_{uncorrected}$	mm	mm	mm
1	0.000	2	0.000	1708	0.000	0.000	0.000	36.09	Inf	0.000	−42	−25	10
						0.000	0.000	27.09	Inf	0.000	−60	−25	10
			0.000	1712	0.000	0.000	0.000	32.96	Inf	0.000	42	−25	10
						0.000	0.000	31.48	Inf	0.000	48	−19	1
						0.000	0.000	28.88	Inf	0.000	54	−25	10
2	0.000	6	0.000	2295	0.000	0.000	0.000	30.81	Inf	0.000	−42	14	−5
						0.000	0.000	28.25	Inf	0.000	−54	8	7
						0.000	0.000	26.77	Inf	0.000	−42	2	7
			0.000	923	0.000	0.000	0.000	17.72	Inf	0.000	−3	8	49
			0.000	535	0.000	0.000	0.000	15.93	Inf	0.000	36	17	4
						0.000	0.000	15.12	Inf	0.000	42	20	−2
						0.000	0.000	10.01	7.66	0.000	45	2	7
3	0.000	6	0.000	1218	0.000	0.000	0.000	25.40	Inf	0.000	−54	−31	−14
						0.000	0.000	21.29	Inf	0.000	−63	−25	−14
			0.000	933	0.000	0.000	0.000	19.40	Inf	0.000	51	−22	−14
						0.000	0.000	14.11	Inf	0.000	48	−7	−14
			0.000	70	0.000	0.000	0.000	7.82	6.49	0.000	12	−28	22
4	0.000	4	0.000	2932	0.000	0.000	0.000	31.88	Inf	0.000	30	−61	−17
						0.000	0.000	24.87	Inf	0.000	30	−52	−23
						0.000	0.000	19.24	Inf	0.000	42	−82	−5
			0.000	898	0.000	0.000	0.000	18.13	Inf	0.000	−27	−58	−17
						0.000	0.000	8.64	6.960	0.000	−36	−85	4
						0.000	0.000	6.89	5.900	0.000	−27	−82	22
5			0.000	2937	0.000	0.000	0.000	39.06	Inf	0.000	12	38	1
						0.000	0.000	36.18	Inf	0.000	21	35	−11
						0.000	0.000	35.68	Inf	0.000	−12	38	4
6	0	6	0.000	3000	0.000	0.000	0.000	44.57	Inf	0.000	−3	−55	31
						0.000	0.000	36.54	Inf	0.000	9	−58	31
						0.000	0.000	19.68	Inf	0.000	−39	−70	37
			0.000	303	0.000	0.000	0.000	18.30	Inf	0.000	51	−64	31
			0.000	84	0.000	0.000	0.000	9.76	7.54	0.000	21	−94	7
			0.000	79	0.000	0.000	0.000	9.29	7.3	0.000	−21	29	46
			0.000	119	0.000	0.000	0.000	9.28	7.3	0.000	0	56	7
						0.000	0.000	7.59	6.34	0.000	−3	56	−8
			0.000	76	0.000	0.000	0.000	9.21	7.26	0.000	24	32	49

A first interpretation of the findings is of dynamic reallocation of cognitive resources during resting state and task performance, such that certain processes are present both during resting and task periods. In particular this is the case for sustained signal intensity in the ACC (as previously described by McKiernan et al., 2003; Sridharan et al., 2008 in healthy individuals). We now suggest that the SZ patients may have failed to reallocate cognitive resources from a resting state situation to an active processing situation due to sustained hyper-activation of the default mode network (c.f. Pomarol-Clotet et al., 2008; Kim et al., 2009a; Whitfield-Gabrieli et al., 2009). This could also explain the often reported finding that patients with schizophrenia are impaired compared to HCs on most cognitive functions, including perception, attention, and executive functions (c.f. Saccuzzo et al., 1982; Berndl et al., 1986; Green et al., 2000; Rund et al., 2006; Harvey, 2010) seen in standard neuropsychological tests.

An interesting finding is the observation of sustained signal intensity in the ACC in the IC5-aDMN component. ACC is typically activated during periods of active processing or task presence (Bush et al., 2000 for review; Diwadkar et al., 2011). However the role of the ACC during periods of resting, or task absence, is not clear. Raichle et al. (2001) did not include the ACC in the default mode network in the 2001 publication, but it is today consensus that the default mode network exists of several networks where ACC is one of the nodes. Current data suggest that the default mode network consists of primary and secondary sub-networks, where the ACC is believed to belong to the primary default mode network (see for example Mannell et al., 2010). Camchong et al. (2011) suggested that the ACC is a region comprising of the default

Table 4 | The table visualizes the components degree of activation among the two groups.

IC	ON-OFF HC	ON-OFF SZ	SEM HC	SEM SZ	Rank sum *z*	Rank sum *p*
1	−0.001	0.001	0.003	0.003	−0.35	0.362
2	0.003	−0.003	0.002	0.003	1.816	0.035
3	0.002	−0.002	0.003	0.003	1.323	0.093
4	−0.007	0.007	0.003	0.003	−3.055	0.001
5	−0.007	0.007	0.004	0.003	−2.745	0.003
6	0.001	−0.001	0.003	0.003	0.451	0.326

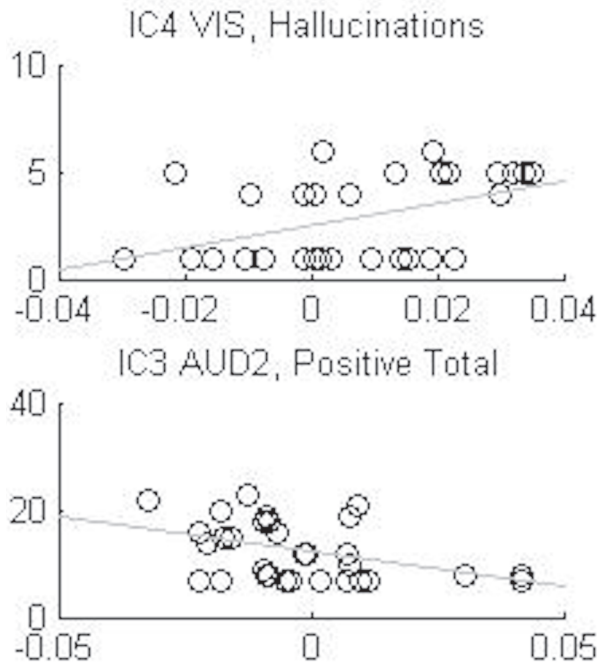

FIGURE 2 | Shows the anomalies in the distributions of the two significant correlations, IC3 auditive component (AUD2) with the sum total of positive symptoms and the IC4 visual component (VIS) with the hallucination symptom, from Table 5.

mode network, which will also show signal intensity during cognitive processing. Thus, increased ACC signal intensity in the SZ group in the task-negative networks, and decreased signal intensity in the positive networks may reflect hyper- versus hypo-activation of the ACC in schizophrenia during periods of task absence or resting versus periods of active task processing, respectively. Seen as such, the ACC may have a dual role as a cognitive hub during both absence of a stimulus and periods of active processing in the presence of a stimulus or task instruction, and that schizophrenia patients show impairments of ACC activation for both passive and active processing (c.f. Sridharan et al., 2008; Guerrero-Pedraza et al., 2011).

Other components that showed significantly more signal intensity by the SZ group in the task-negative networks were the visual component, IC4-VIS. One of the main nodes in this network, the fusiform gyrus, has been found to be reduced in schizophrenia patients compared to HCs (Takahashi et al., 2006). Furthermore, increased signal intensity has also been reported in this area by Lagioia et al. (2010), though in persons with schizotypal personality trait expression. However we do believe that their explanation also can be a possible explaining for our findings, particularly in patients with frequent positive symptoms that could be thought of as engaging a mental imagery component.

Turning to the component showing a significant group difference in the executive component, IC2-EXE, the hypo-frontal signal intensity in the SZ group is similar to what has been frequently reported in the literature of impaired prefrontal function in schizophrenia to cognitive task processing (see for example Fu et al., 2005). The IC2-EXE component extended into the Insula, SMA, and ACC. As mentioned by Craig (2009), joint signal intensity of the Insula and the ACC are commonly reported in most studies. The Insula has shown signal intensity with fMRI during affective-, cognitive-, and aversive interceptive processing and therefore claimed for linking emotions to cognitive processes and behavior responses (Paulus and Stein, 2006), but the Insula has also been suggested to be part of representation of awareness (Craig, 2009). Further Bush et al. (2000, review) summarized the ACC to serve as a monitor for crosstalk between brain areas related to conflict and competition. We would like to extend this by suggesting that failure in the ACC signal intensity in the SZ group when required for active processing may be related to the general deficit in cognitive processing seen in schizophrenia. Kim et al. (2009b) also mentioned in their paper that the ACC, but also the DLPFC, did seem to overlap in their components of relevance. The signal they detected in a component consisting of ACC, DLPFC, thalamus, and Insula, was reported in their paper with higher signal intensity in their controls than their patients (schizophrenia and schizoaffective persons), which also were quite similar to our findings in the IC2-EXE component.

As also discussed by Sridharan et al. (2008) we believe that the ACC may be of particular interest concerning the dynamic shift between default mode and executive networks, acting like a gate-keeper or switch (c.f.r. Kim et al., 2009b). The existence of alterations in dynamic networks connectivity has previously been suggested to be one of the reasons for developing more severe symptoms in the schizophrenia patients (Arnsten et al., 2010). We suggest that an alteration in the ACC alone may contribute to different symptoms depending on which brain structures such alteration further influences (see also van Veen and Carter, 2002). There seems to be consensus in the literature that the default mode network is up-regulated in the schizophrenia patients compared to HCs, whereas the executive network is down-regulated (however see Fu et al., 2005 for other interpretations).

A limitation of the present results is that when using a brain template, individual changes in brain anatomy among participants may influence location and degree of the brains signal intensity. This would be most prominent for the patient group since brain anatomy changes have commonly been reported in this group (see review by McCarley et al., 1999; Takahashi et al., 2006). Moreover it is unclear what effect antipsychotic medication may have on brain structure and function (see, e.g., recent longitudinal studies by Ho et al., 2011; van Haren et al., 2011). Lastly, the

Table 5 | The table visualizes the correlation coefficients between PANSS parameters and BOLD activation for the different ICs and the corresponding *p*-values.

Symptoms	IC1-AUD1		IC2-EXE		IC3-AUD2		IC4-VIS		IC5-aDMN		IC6-pDMN	
	r-Value	*p*-Value	*r*-Value	*p*-Value	*r*-Value	*p*-Value	*r*-Value	*p*-Value	*r*-Value	*p*-Value	*r*-Value	*i*-Value
Hallucination	−0.088	0.639	−0.353	0.051	−0.349	0.054	**0.440**	**0.013**	0.031	0.868	0.167	0.370
Duration	−0.081	0.663	−0.064	0.731	−0.261	0.157	0.145	0.436	0.090	0.630	−0.168	0.365
Neg_T	−0.064	0.731	−0.100	0.592	−0.163	0.382	−0.058	0.756	0.070	0.710	−0.267	0.146
Pos_T	−0.076	0.684	−0.281	0.126	**−0.412**	**0.021**	0.351	0.053	0.020	0.915	0.090	0.629
Gen_T	0.115	0.537	−0.085	0.650	−0.088	0.639	0.039	0.835	−0.128	0.494	0.049	0.792
PANSS_T	−0.006	0.973	−0.207	0.263	−0.294	0.109	0.141	0.449	−0.017	0.927	−0.061	0.743

*Capital T stands for total. The coefficients in bold font are significant, $p < 0.05$, but these correlations were driven by anomalies in the distribution (see **Figure 2** for details).*

heterogeneity of symptoms in the SZ group could have influence on the results.

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Working memory related brain network connectivity in individuals with schizophrenia and their siblings

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A growing number of studies have reported altered functional connectivity in schizophrenia during putatively "task-free" states and during the performance of cognitive tasks. However, there have been few systematic examinations of functional connectivity in schizophrenia across rest and different task states to assess the degree to which altered functional connectivity reflects a stable characteristic or whether connectivity changes vary as a function of task demands. We assessed functional connectivity during rest and during three working memory loads of an *N*-back task (0-back, 1-back, 2-back) among: (1) individuals with schizophrenia ($N = 19$); (2) the siblings of individuals with schizophrenia ($N = 28$); (3) healthy controls ($N = 10$); and (4) the siblings of healthy controls ($N = 17$). We examined connectivity within and between four brain networks: (1) frontal–parietal (FP); (2) cingulo-opercular (CO); (3) cerebellar (CER); and (4) default mode (DMN). In terms of within-network connectivity, we found that connectivity within the DMN and FP increased significantly between resting state and 0-back, while connectivity within the CO and CER decreased significantly between resting state and 0-back. Additionally, we found that connectivity within both the DMN and FP was further modulated by memory load. In terms of between network connectivity, we found that the DMN became significantly more "anti-correlated" with the FP, CO, and CER networks during 0-back as compared to rest, and that connectivity between the FP and both CO and CER networks increased with memory load. Individuals with schizophrenia and their siblings showed consistent reductions in connectivity between both the FP and CO networks with the CER network, a finding that was similar in magnitude across rest and all levels of working memory load. These findings are consistent with the hypothesis that altered functional connectivity in schizophrenia reflects a stable characteristic that is present across cognitive states.

Keywords: schizophrenia, functional connectivity, working memory, cognitive control, cerebellum, task, risk

INTRODUCTION

A growing body of work focused on understanding the neurobiological bases of cognitive impairment in schizophrenia suggests that changes in the function of a single brain region, or even a brain system, cannot explain the functional impairments seen in this illness. Instead, research has increasingly focused on understanding the integrity of neural circuits that work together to support sensory, cognitive, and emotional processes (Calhoun et al., 2009). This approach to understanding schizophrenia is consistent with the hypothesis that this illness reflects a "dysconnection" syndrome (Stephan et al., 2009). Much of this work has focused on examining different aspects of functional brain connectivity, either when the individual is at rest, or when the individual is performing a specific task (e.g., working memory). Both types of studies have provided robust evidence for altered functional connectivity in schizophrenia (Brown and Thompson, 2010). However, few studies have examined functional connectivity in schizophrenia across both resting and active task states. As such, it is difficult to know to what degree such impairments are state dependent or reflective of more fundamental and stable changes in brain organization in schizophrenia. Thus, the goal of the current study was to examine functional brain connectivity in known neural networks during rest and during different working memory loads in individuals with schizophrenia, their siblings, and healthy controls.

Functional brain connectivity is an approach to understanding brain function that examines the covariance in activity across brain regions. One common approach to assessing connectivity is to use blood oxygen level dependent (BOLD) timeseries acquired using fMRI (often referred to as fcMRI), either while the person is resting or while the person is engaged in a particular task. FcMRI data can be analyzed in a variety of ways, including hypothesis driven approaches that start with the identification of one or more regions of interest (ROIs) and either examine the covariance of a timeseries from this region with all other voxels in the brain or with the timeseries from specific other ROIs. Alternatively, one can use a more data driven approach, such as independent components analysis, that identifies groups of brain regions showing covarying timeseries at differing spatial scales. One hypothesis about the

meaning of fcMRI is that it identifies brain regions that have a history of "working together" and that likely reflect a combination of both structural connectivity and more indirect connections (Fair et al., 2007a,b,c; Dosenbach et al., 2010). It is conceptually similar to other measures of assessing coordinated activity across the brain, such as EEG coherence, but differs in the time scale (on the order of seconds for fcMRI versus milliseconds for EEG coherence) and spatial resolution (higher for fcMRI than EEG coherence).

As noted above, numerous studies have now examined functional brain connectivity in schizophrenia during rest states. Several of these studies have examined characteristics of functional brain connectivity using graph theoretic approaches. These studies have found evidence for altered "small-world" network characteristics in schizophrenia, including reduced efficiency, increased path lengths, and reduced clustering coefficients (Bassett et al., 2008; Liu et al., 2008; Lynall et al., 2010; Yu et al., 2011). Other work has provided evidence for reduced global brain connectivity in dorsolateral prefrontal regions (Cole et al., 2011). Additional studies have focused on specific brain networks. For example, our previous work has examined connectivity within and between four replicable brain networks thought to be critical for cognitive function; (1) a "default mode" network (DMN; Damoiseaux et al., 2006; Raichle and Snyder, 2007) consisting of brain regions that reduce their activity during active cognitive demands; (2) a dorsal fronto-parietal network (FP) activated by a range of cognitive control tasks (Dosenbach et al., 2006, 2007, 2008; Fair et al., 2007b); (3) a cingulo-opercular network (CO) thought to be involved in task set maintenance and error processing (Dosenbach et al., 2006, 2007, 2008; Fair et al., 2007b; Becerril et al., 2011); and (4) a cerebellar network (CER) that shows error related activity in many different types of tasks (Dosenbach et al., 2006, 2007, 2008; Fair et al., 2007b; Becerril et al., 2011). We found intact connectivity within each of these four networks among individuals with schizophrenia and their siblings, but reduced connectivity between all three control networks (FP, CO, and CER). Other studies have also found abnormal resting state connectivity in regions involved in the FP, CO, and CER networks (Zhou et al., 2007; Jafri et al., 2008; Welsh et al., 2008; Bassett et al., 2011; Woodward et al., 2011; Zalesky et al., 2011; Tu et al., 2012). Although we did not find functional connectivity changes with the DMN or between the DMN and other networks, other studies have found such alterations (Bluhm et al., 2007, 2009; Jafri et al., 2008; Whitfield-Gabrieli et al., 2009; Mannell et al., 2010; Rotarska-Jagiela et al., 2010; Salvador et al., 2010; Camchong et al., 2011; Chai et al., 2011).

Because these studies have measured connectivity at "rest," the typical interpretation has been that these changes in schizophrenia represent stable alterations in brain connectivity. However, one of the challenges of studying "rest" states is that connectivity changes could reflect differences in the cognitive states of the individuals, rather than stable structural or functional changes in brain connectivity. For example, if there were systematic differences in what individuals with schizophrenia were thinking about during rest (e.g., related to delusional or hallucinatory material, etc.; Sutton, 1973) or even during task states, this could lead to the appearance of altered functional connectivity. If such resting state changes in connectivity were due to such confounds, one might expect group differences in connectivity to be reduced (or at least altered) when participants were asked to engage in a specific task that imposed structure on the mental state of the individual. In contrast, if similar patterns of altered connectivity were found in resting state and during cognitive task performance in schizophrenia, it would provide support to the hypotheses that such connectivity changes reflect fundamental alterations in brain connectivity.

A number of studies have also examined functional connectivity during structured cognitive tasks in schizophrenia. A few of these studies have provided evidence for altered small-world characteristics during task states (Micheloyannis et al., 2006; Yu et al., 2011). However, most task-based functional connectivity studies have focused on specific regions or brain networks. These studies have provided evidence for alterations in functional connectivity across a range of tasks (Anticevic et al., 2011; Diaconescu et al., 2011; Fornito et al., 2011; Mukherjee et al., 2011), with working memory paradigms receiving the greatest focus. These studies have provided further evidence for connectivity changes in regions associated with the DMN, FP, CO, and CER networks, though the specific patterns of increased and decreased connectivity in schizophrenia have varied across studies (Meyer-Lindenberg et al., 2001, 2005; Schlosser et al., 2003a,b; Barch and Csernansky, 2007; Crossley et al., 2009; Henseler et al., 2010; Kang et al., 2011; White et al., 2011). Several of studies have either examined connectivity during a single task condition or integrated across conditions (Schlosser et al., 2003a,b; Barch and Csernansky, 2007; Crossley et al., 2009; Wolf et al., 2009), or found similar pattern of connectivity across task conditions (Meyer-Lindenberg et al., 2001). Such results could be consistent with the hypothesis that functional connectivity changes in schizophrenia reflect stable changes in brain connectivity. However, without a specific comparison to resting state conditions or between very different task conditions, it is difficult to know whether these are more state or trait related changes. Other studies have found evidence for different patterns of functional connectivity during different working memory task conditions (e.g., as a function of load, stimulus type, or task phase; Meyer-Lindenberg et al., 2005; Henseler et al., 2010; Kang et al., 2011; Rasetti et al., 2011). Such findings suggest that functional connectivity changes could reflect differences in task engagement or responsivity of brain networks to modulation, rather than stable changes that persist across all task states.

What is needed to help address these questions is a systematic examination of functional connectivity in schizophrenia across rest and across different task states to assess the degree to which altered functional connectivity reflects a trait like characteristic that is present regardless of the mental or behavioral state of the individual, or whether connectivity changes vary as a function of task demands. One previous fMRI study tried to examine this question in schizophrenia, comparing global brain connectivity across verb generation, an *N*-back working memory task, and rest (Salomon et al., 2011). These researchers found wide spread evidence for reduced functional connectivity, with the greatest differences during rest. However, interpretation of the results of this study are dramatically limited by the very small sample sizes, the fact that the same individuals did not participate in both the task and resting state experiments (meaning that state differences could reflect person differences), and by the failure to assess a number of potential methodological confounds (e.g., increased movement

in patients). An EEG connectivity study also examined graph theoretic measures during rest and during a working memory task in schizophrenia. These researchers found reduced cluster coefficients among schizophrenia individuals during both rest and task in the alpha, beta and gamma bands, but only found increased path lengths during rest states (Micheloyannis et al., 2006).

The goal of the current study was to address questions related to the state dependence of functional connectivity changes in schizophrenia by comparing functional connectivity within and between four brain networks (DMN, FP, CO, and CER) during rest and during three different levels of working memory load between individuals with schizophrenia, their siblings, and healthy controls. We focused on working memory because of the consistent evidence for impairment in this cognitive domain in schizophrenia (Forbes et al., 2009), the fact that the largest number of task-based connectivity studies in schizophrenia have focused on working memory, and due to existing previous work in healthy individuals examining connectivity changes as a function of memory load during working memory. Specifically, Newton et al. (2011) recently demonstrated that brain regions within the FP and DMN networks showed increases in functional connectivity as working memory load increased, suggesting dynamic modulation of functional coupling among brain regions as task demands changes. We predicted that if functional connectivity changes in schizophrenia reflect stable changes in brain connectivity, we should see similar patterns of functional connectivity alterations across rest and across working memory loads. However, if at least some functional connectivity changes in schizophrenia reflect a failure to appropriately modulate brain networks as a function of changing task demands, then we may see increases in functional connectivity alterations in schizophrenia with increasing memory load or control demands.

MATERIALS AND METHODS

PARTICIPANTS

The participants (**Table 1**) for this study were recruited through the Conte Center for the Neuroscience of Mental Disorders (CCNMD) at Washington University School of Medicine in St. Louis included: (1) individuals with DSM-IV Schizophrenia (SCZ; $N = 19$); (2) the non-psychotic siblings of individuals with schizophrenia (SCZ-SIB; $N = 28$); (3) healthy controls (CON; $N = 10$); and (4) the siblings of healthy controls (CON-SIB; $N = 17$). Siblings were full siblings, based on self-report. These participants were a largely overlapping subset of participants reported on in our previous paper on resting state connectivity (Repovs et al., 2011) who had both resting state connectivity data and *N*-back working memory data. All participants gave written informed consent for participation and all participants had been included in our previous report on resting state functional connectivity changes in schizophrenia (Repovs et al., 2011). The average duration of illness for the individuals with schizophrenia was 4.79 (SD = 2.98). Fifteen of the individuals with schizophrenia were taking atypical antipsychotics, and four were taking both typical and atypical antipsychotics.

All subjects were diagnosed on the basis of a consensus between a research psychiatrist who conducted a semi-structured interview and a trained research assistant who used the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 2001). Participants were excluded if they: (a) met DSM-IV criteria for substance dependence or severe/moderate abuse during the prior 6 months; (b) had a clinically unstable or severe medical disorder; (c) had a history of head injury with documented neurological sequelae or loss of consciousness; or (d) met DSM-IV criteria for mental retardation.

The individuals with schizophrenia were all outpatients, and were stabilized on antipsychotic medication for at least 2 weeks. Controls were required to have no lifetime history of Axis I psychotic or mood disorders and no first-degree relatives with a psychotic disorder. Potential SCZ-SIB subjects were excluded if they had a lifetime history of any DSM-IV Axis I psychotic disorder, but not other DSM-IV Axis I disorders. CON-SIB subjects were enrolled in an identical manner to SCZ-SIB subjects, and met the same general and specific inclusion and exclusion criteria, other than the requirement to have a sibling with schizophrenia. The siblings of healthy controls had the following diagnoses: (1) previous substance abuse ($N = 4$, 24%); (2) previous substance dependence ($N = 1$, 6%); (3) major depression ($N = 3$, 18%); and (4) social phobia ($N = 1$, 6%). The siblings of schizophrenia patients had the following diagnoses: (1) previous substance abuse ($N = 6$, 21%); (2) previous substance dependence ($N = 2$, 7%); (3) bipolar II disorder ($N = 1$, 7%); (4) major depression ($N = 6$, 21%); (5) social phobia ($N = 1$, 7%); and (6) PTSD ($N = 1$, 7%).

CLINICAL AND COGNITIVE ASSESSMENTS

Psychopathology and cognitive function outside of the MR scanner were assessed as previously described (Delawalla et al., 2006; Harms et al., 2007) and as described in the Supplemental Materials. Scores for each symptom domain and each cognitive domain are shown in **Table 1**.

fMRI SCANNING

All scanning occurred on a 3T Tim TRIO Scanner at Washington University Medical School. Functional images (BOLD) were acquired using an asymmetric spin-echo, echo-planar sequence [$T2^*$; repetition time (TR) = 2500 ms, echo time (TE) = 27 ms, field of view (FOV) = 256 mm, flip = 90°, voxel size = 4 mm × 4 mm × 4 mm]. Resting state data were acquired from each participant for two BOLD runs in which participants rested quietly with their eyes closed. Each run contained 164 images, for a total of 328 images and 13.7 min of resting state activity. Working memory task data were acquired from each participant in three BOLD runs, each consisting of two blocks of 0-back, 1-back, or 2-back working memory task. Each run consisted of 137 images (105 of them acquired during task performance), for a total of 411 images (315 acquired during task performance) and 17.1 min of scanning (13.1 min of task performance). In addition, a T1 structural image was acquired using a sagittal MP-RAGE 3D sequence (TR = 2400 ms, TE = 3.16 ms, flip = 8°; voxel size = 1 mm × 1 mm × 1 mm).

N-BACK WORKING MEMORY TASK

All subjects performed one run of each of three levels of an "*N*-back" working memory task in which their task was to respond for each letter shown whether it was the same as a pre-specified

Table 1 | Demographic, clinical, and performance characteristics of study participants.

Measure	Group							
	Healthy controls (CON)		Siblings of controls (CON-SIB)		Individuals with schizophrenia (SCZ)		Siblings of schizophrenia (SCZ-SIB)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	24.3	2.7	22.6	2.8	24.4	3.4	24.2	3.6
Gender (% male)	60		61		72		58	
Education	15	1.8	13.9	1.6	12.3	1.9	13.4	2.5
Parental education	15.3	1.7	14.4	1.5	14.2	2.1	15	2.3
Negative symptoms*	−0.42	0.20	−0.33	0.42	1.13[a]	0.75	−0.13	0.53
Positive symptoms*	−0.51	0.10	−0.32	0.41	1.08[a]	1.10	−0.27	0.30
Disorganization symptoms*	−0.33	0.28	−0.26	0.25	0.73[a]	0.98	−0.15	0.35
***N*-BACK PERFORMANCE**								
0-back accuracy	0.81	0.05	0.88	0.04	0.72	0.03	0.83	0.03
1-back accuracy	0.82	0.04	0.87	0.03	0.68	0.03	0.83	0.03
2-back accuracy	0.80	0.06	0.86	0.05	0.64	0.04	0.76	0.04
NEUROPSYCHOLOGICAL ASSESSMENT								
IQ^	0.21	0.54	−0.42	0.76	−0.91[a]	0.67	−0.34	0.76
Working memory^	0.82	0.66	0.53	0.56	−0.52[a]	0.63	0.23[c]	0.72
Episodic memory^	0.74	0.84	0.44	0.53	−0.89[a]	0.44	−0.03[b]	0.57
Executive function^	−0.76	0.38	0.55	0.39	−0.38[a]	0.85	−0.14[b]	0.47

The four groups did not differ significantly in age [$F(3, 70) = 1.2$, $p > 0.10$], parental education [$F(3, 70) = 0.96$, $p > 0.50$], gender ($X^2 = 2.5$, $p > 0.4$), or race ($X^2 = 7.2$, $p > 0.3$). The groups did differ in personal education [$F(3, 70) = 4.06$, $p < 0.05$], with the SCZ having fewer years of education than CON. The Ns for SCZ and SCZ-SIB and for CON and CON-SIB are not identical given that some participants were excluded for failure to complete the entire protocol or excessive movement. Of the 101 participants aged 18 or older from whom we collected resting state data, there were 12 who had to be excluded for poor quality imaging data (4 SCZ, 4 SCZ-SIB, 1 CON, and 3 CON-SIB) and 15 who were excluded because they did not have N-back data (6 SCZ, 3 SCZ-SIB, 5 CON, and 1 CON-SIB).

**Symptom scores are reported in Z scores relative to the mean of the entire sample. See Section "Materials and Methods" for details. One-way ANOVAs indicated significant group differences for positive [$F(3, 70) = 25.14$, $p < 0.001$], negative [$F(3, 70) = 3 - 0.88$, $p < 0.001$], and disorganization [$F(3, 70) = 13.57$, $p < 0.001$] symptoms. [a]Post hoc contrasts using Tukey's HSD indicated that the SCZ had higher scores on all three symptom domains, with no significant differences among the remaining groups.*

^Cognitive scores are reported in Z scores relative to the mean of the entire sample. See Section "Materials and Methods" for details. One-way ANOVAs indicated significant group differences for IQ [$F(3, 70) = 5.69$, $p < 0.001$], working memory [$F(3, 70) = 12.06$, $p < 0.001$], episodic memory [$F(3, 70) = 23.7$, $p < 0.001$], and executive function [$F(3, 70) = 11.96$, $p < 0.001$]. [a]Post hoc contrasts using Tukey's HSD indicated that the SCZ participants had worse performance in all four cognitive domains than CON and CON-SIB. [b]SCZ-SIB performed worse than CON on executive function and episodic memory, and showed a [c]trend for reduced performance on working memory ($p < 0.10$).

letter (e.g., "X"; 0-back), the same as the immediately preceding letter (1-back), or the same as the letter shown two trials previously (2-back). Each of the memory loads was performed for two task blocks within the same run and the order of runs was counterbalanced across participants. The task followed a mixed state-item design. Each block started with a cue shown for 2.5 s indicating the *N*-back condition, followed by letters presented one at a time for 2.5 s each. The delay between items was variable with the following proportion of delays 1 TR: 5%, 2 TR: 31%, and 3 TR: 64%. Each task block contained 21 trials and lasted for a total of 105 s. Each run started with 25 s of fixation, and each task block was followed by a 45 s fixation block.

fcMRI DATA PREPROCESSING

Basic imaging data preprocessing included: (1) Compensation for slice-dependent time shifts; (2) Removal of first five images from each run during which BOLD signal was allowed to reach steady state; (3) Elimination of odd/even slice intensity differences due to interpolated acquisition; (4) Realignment of data within and across runs to compensate for rigid body motion (Ojemann et al., 1997); (5) Intensity normalization to a whole brain mode value of 1000; (6) Registration of the 3D structural volume (T1) to the atlas representative template in the Talairach coordinate system (Talairach and Tournoux, 1988) using a 12-parameter affine transform; and (7) Co-registration of the 3D fMRI volume to the structural image and transformation to atlas space using a single affine 12-parameter transform that included a re-sampling to a 3-mm cubic representation.

To improve signal-to-noise, remove baseline, possible sources of spurious correlations, and task structure, all images were further preprocessed in steps that included: (1) spatial smoothing using a gaussian kernel with three voxels FWHR, (2) high-pass filtering with 0.009 Hz cutoff frequency[1], (3) removal of nuisance

[1]In prior work Repovs et al. (2011), we compared using just a high-pass filter and both a high and low-pass filter, finding identical results with both approaches. Thus,

signal that included six rigid body motion correction parameters, ventricle, white matter, and whole brain signals, as well as their first derivatives. In task data the additional regressors included sustained task activity, modeled using assumed-response Boynton HRF function (Boynton et al., 1996), and transient response activity, modeled as unassumed response spanning nine frames. Task response was modeled separately for each of the task levels. All connectivity analyses were conducted on residual timeseries after removal of listed regressors.

A frequent confound in imaging studies with clinical populations is that the clinical group moves more, which can lead to lower signal-to-noise ratio (SNR) in the acquired resting state data, and perhaps also apparent reductions in connectivity. Thus, we took two approaches to addressing movement-related confounds. First, we directly compared the four groups on average SNR during the resting state runs and during the working memory runs. SNR was computed as the mean value for each slice across each run, divided by the standard deviation across the frames in the run. We then averaged the SNR values across slices and runs within either resting state or working memory. We used a repeated measures ANOVA with condition (rest versus task) as a within subject factor, and genetic liability as a between subject factor. There was a significant main effect of condition [$F(1, 70) = 20.4$, $p < 0.001$], with lower SNR in rest versus task. This finding is consistent with the fact that movement tends to increase the longer individuals are in the MR scanner, and participants completed the resting state scans after the working memory scans. There was no significant main effect of genetic liability [$F(3, 70) = 1.3$, $p = 0.27$], and no significant interaction between condition and genetic liability [$F(3, 70) = 2.2$, $p = 0.09$]. Second, as a last preprocessing step, frames with excessive movement and movement-related intensity changes were identified and excluded from further analysis. Bad frames were identified following a modified procedure suggested by Power et al. (2011) as those that met at least one of the two criteria. First, frames in which sum of the displacement across all six rigid body movement correction parameters exceeded 0.5 mm were identified. Second, root mean square (RMS) of differences in intensity between the current and preceding frame was computed across all voxels and divided by mean intensity. Frames in which normalized RMS was more than 1.6 the median across the run were identified. The identified frames, one preceding and two following frames were then marked for exclusion in computation of functional connectivity. A repeated measures ANOVA for the percentage of eliminated frames, with run type (rest, working memory) as a within subject factor and group (SCZ, SCZ-SIB, CON, CON-SIB) as a between subject factor, indicated a main effect of group [$F(3, 70) = 3.98$, $p < 0.05$], but no main effect of run type [$F(1, 70) = 0.02$, $p > 0.5$] and no interaction between group and run type [$F(3, 70) = 0.43$, $p > 0.5$]. *Post hoc* tests using Tukey's HSD indicated that SCZ ($M = 9.4\%$, SD = 7.7%) had more eliminated trials than CON-SIB ($M = 1.6\%$, SD = 2.2%), but no further significant differences from either SCZ-SIB ($M = 6.2\%$, SD = 9.11%) or CON ($M = 3.6\%$, SD = 3.0%).

we used only the high-pass filter approach here to be consistent with our prior resting study connectivity study on these individuals.

For resting state data, the two BOLD timeseries (excluding the first five frames) were concatenated to form a single timeseries. For task-based data, only task-related parts of the BOLD timeseries were used. Due to the delay in HRF, the first three frames after task onset were excluded, and one frame after the end of task block were included in the timeseries. The initial BOLD preprocessing was accomplished using in-house software, fcMRI preprocessing and analyses described below were performed using custom Matlab (The Mathworks, Natick, Massachusetts) code.

NETWORK REGION DEFINITION

We examined regions included in the DMN as defined by Fox et al. (2005), and regions included in the FP, CO, and CER networks as defined by Dosenbach et al. (2007). To control for individual anatomical variability, ROI were defined for each individual in two steps. First, we created spherical ROIs in standard Talairach space centered on the reported coordinates for each region (**Figure 1**; Table S1 in Supplementary Material) and 15 mm in diameter. Second, we masked the resulting group ROIs with the individual FreeSurfer (http://surfer.nmr.mgh.harvard.edu, version 4.1.0) segmentation of a high-resolution structural image that was previously registered to standard Talairach space, excluding any voxels within the group defined ROIs that did not represent the relevant gray matter (cerebral cortex, cerebellar cortex, hippocampus, thalamus) in the specific individual, as defined by FreeSurfer (Fischl et al., 2002). Given that we used *a priori* ROIs, we conducted a number of analyses in the control subjects using these ROIs to validate the expected pattern of connectivity within and between these four networks. The results of these analyses are presented in the supplement.

DATA ANALYSIS

We extracted the time series for each of the ROIs described above and computed the ROI–ROI correlation matrix for each participant, separately for resting state (R), and 0-back (0B), 1-back (1B) and 2-back (2B) task-based data. We then converted correlations to Fisher z-values using Fisher r-to-z transform and computed the average connectivity (mean Fisher z-value) across all ROI–ROI connections within each of the four networks, and computed the average connectivity across all ROI–ROI connections between each network. We denoted within-network averages as wDMN, wFP, wCO, and wCER, and between network connectivity averages as bDMN-FP, bDMN-CO, bDMN-CER, bFP-CO, bFP-CER, and bCO-CER. We estimated group-level statistical significance by using the resulting Fisher-z values as the dependent measure in the second-level analysis.

To compare the groups and assess the effect of task on connectivity within and between networks we analyzed the results in two phases. First, we focused on comparison between rest and task (0B), and second, on the effect of working memory load (0B, 1B, 2B) in both cases using separate mixed design ANOVAs for exploring within and between network connectivity. In the ANOVA presented below, we include a between subject factor that we call genetic liability, to indicate that the participants were either individuals with schizophrenia or their siblings (SCZ) or healthy controls or their siblings (CON). Thus, these ANOVAs

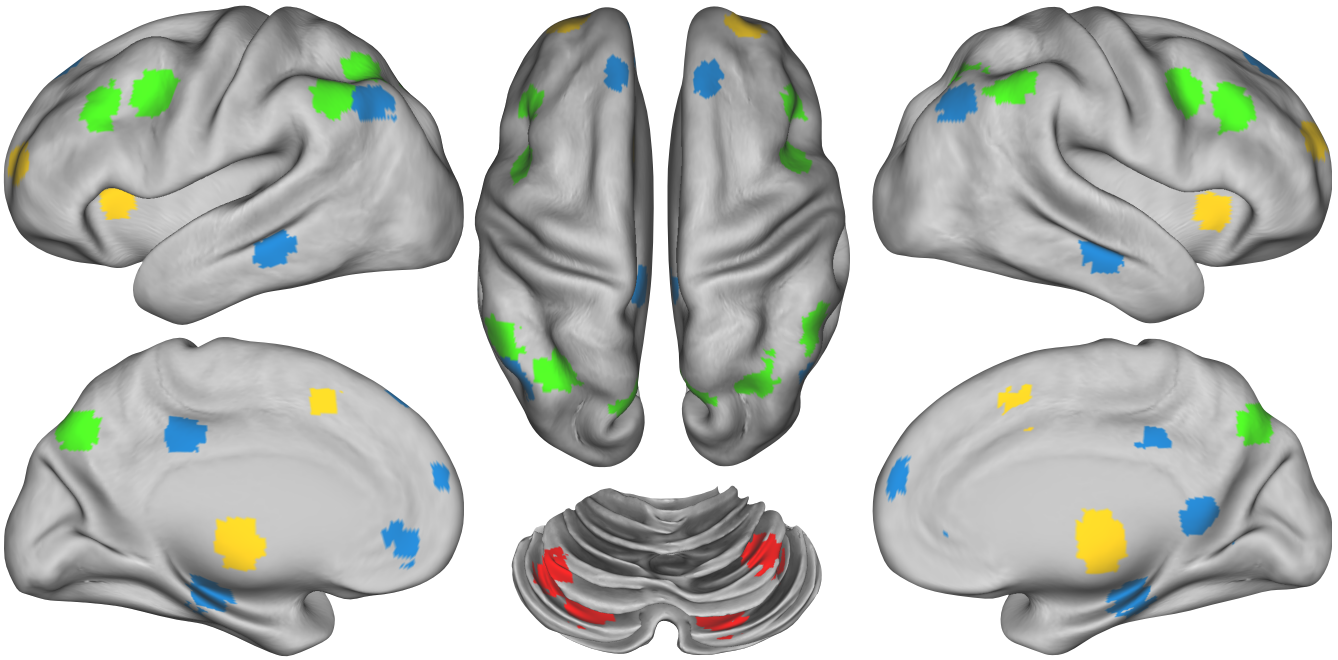

FIGURE 1 | Figure illustrating the location of regions within each of the four networks. Regions of the Frontal–Parietal network (FP) are marked in green, the Cingulo-Opercular network (CO) in yellow, the Default Mode Network (DMN) in blue, and the Cerebellar network (CER) in red.

included genetic liability (SCZ versus CON) and family member type [index (i.e., SCZ or CON) versus sibling (i.e., SCZ-SIB or CON-SIB)] as between subject factors. Significant effects were further explored with planned comparison, using False Discovery Rate to control for multiple comparisons, to isolate the source of significant ANOVA effects. For the sake of brevity, we do not report main effects or interactions that include family member type, but do not also include genetic liability. Statistical analysis was conducted using R (Team, 2011) and visualized using ggplot2 library (Wickham, 2009).

RESULTS

BEHAVIORAL DATA

The accuracy data for the *N*-back task was analyzed using a repeated measures ANOVA with load (0B, 1B, 2B) as a within subject factor, and genetic liability (SCZ or CON) and family member type (index or sibling) as between subject factors. As shown in **Table 1**, this ANOVA revealed a main effect of load [$F(2, 140) = 4.76$, $p < 0.01$], a main effect of genetic liability [$F(1, 70) = 7.48$, $p < 0.01$], a main effect of family member type [$F(1, 70) = 7.05$, $p = 0.01$], and a trend level load by genetic liability interaction [$F(2, 140) = 2.4$, $p = 0.09$]. Accuracy decreased as memory load went up, and the SCZ and SCZ-SIB performed worse than the CON and CON-SIB. The main effect of sibling group indicated that the index siblings performed overall worse. The reaction time data (median correct) also showed a significant main effect of load [$F(2, 140) = 92.0$, $p < 0.001$], but no other significant main effects or interactions. Reaction times increased as a function of memory load across all groups.

TASK VERSUS REST AND WITHIN-NETWORK CONNECTIVITY

The within-network ANOVA for task versus rest included genetic liability (SCZ or CON) and family member type (index or sibling) as between subject factors, and task [0-back (0B) versus rest (R)] and network (wDMN, wFP, wCO, and wCER) as within subject factors. This ANOVA revealed a significant effect of task [$F(1, 70) = 7.82$, $p = 0.006$], a significant effect of network [$F(3, 310) = 52.2$, $p < 0.001$], and a significant task × network interaction [$F(3, 210) = 20.6$, $p < 0.001$]. There were no significant effects of genetic liability, though there was a trend for a three-way interaction between task, network, and genetic liability [$F(3, 210) = 2.29$, $p = 0.08$]. To examine the source of task × network interaction we ran separate ANOVAs for each of the four networks employing FDR correction for multiple comparison across the tests. The results revealed a significant effect of task for all four networks. However the pattern of this effect differed across networks (see **Figure 2** for graphs collapsing across SCZ and SCZ-SIB and CON and CON-SIB; See Figure S4 in Supplementary Material for data plotted for each group individually). There was stronger connectivity within the DMN [$F(1, 70) = 10.4$, $p = 0.002$] and the FP [$F(1, 70) = 4.60$, $p = 0.035$] networks for 0B as compared to rest. In contrast, there was weaker connectivity within the CO [$F(1, 70) = 8.54$, $p = 0.005$] and the CER [$F(1, 70) = 31.7$, $p = 0.001$] networks for 0B compared to rest. The three-way interaction between network, task, and genetic liability was at trend level. This reflected the fact that the follow-up contrasts indicated a task × genetic liability interaction in wDMN [$F(1, 70) = 4.15$, $p = 0.045$] connectivity. Although this effect would not survive FDR correction for multiple comparisons,

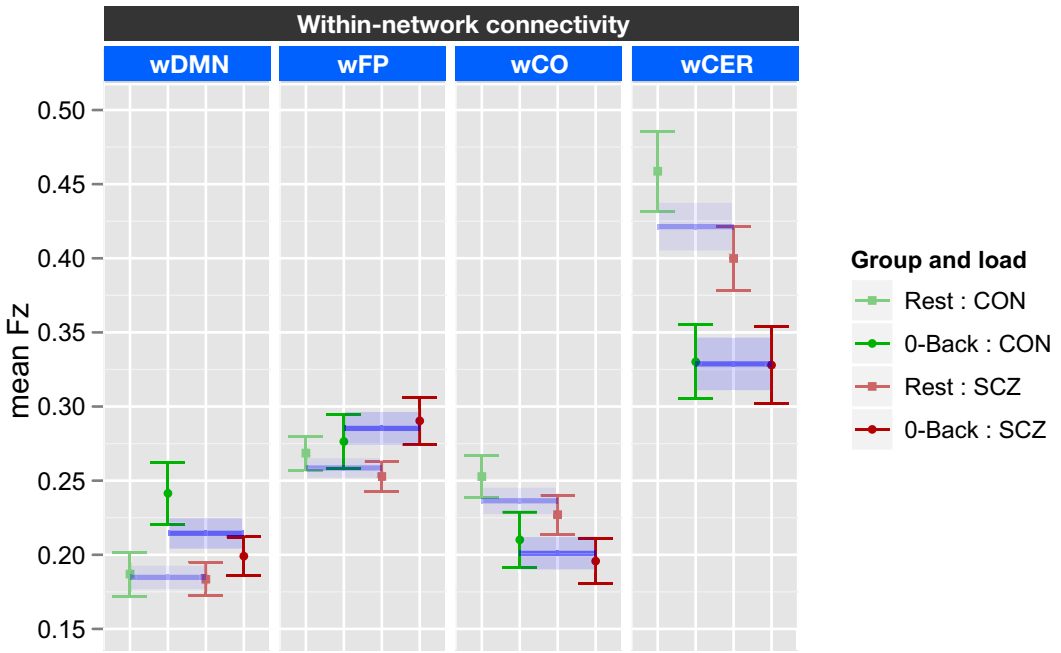

FIGURE 2 | Graph illustrating 0-back task versus rest within-network connectivity collapsed across siblings. SCZ, individuals with schizophrenia and siblings of individuals with schizophrenia; CON, healthy controls and siblings of healthy controls; DMN, Default Mode Network; FP, Frontal–Parietal Network; CO, Cingulo-Opercular Network; CER, Cerebellar Network; w, within. Segments marked in blue indicate networks that showed significant main effects of task (0-back versus rest). The main effect of task is further illustrated by blue lines and shading showing data collapsed across all groups (mean and standard error). See Figure S4 in Supplementary Material for data plotted for each of the four groups separately.

it suggested that SCZ and SCZ-SIB did not show a significant difference between 0B and rest in wDMN connectivity. No other networks demonstrated a significant task by group interaction (all $ps > 0.10$).

TASK VERSUS REST AND BETWEEN NETWORK CONNECTIVITY

The between network ANOVA for task versus rest also included genetic liability and family member type as between subject factors, and task (0B versus rest) and network (bDMN-FP, bDMN-CO, bDMN-CER, bFP-CO, bFP-CER, and bCO-CER) as within subject factors. This ANOVA revealed significant main effects of genetic liability [$F(1, 70) = 14.1$, $p < 0.001$], network [$F(5, 350) = 46.1$, $p < 0.001$], and task [$F(1, 70) = 17.1$, $p < 0.001$] as well as significant task × network [$F(5, 350) = 5.6$, $p < 0.001$] and network × genetic liability [$F(5, 350) = 4.07$, $p = 0.001$] interactions. To follow-up on the significant effects, we ran ANOVAs for each of the six between network connectivities employing FDR correction for multiple comparisons (see **Figure 3**). The significant network by task interaction reflected the fact that there was a significant effect of task for bDMN-FP [$F(1, 70) = 26.6$, $p < 0.0001$], bDMN-CO [$F(1, 70) = 12.9$, $p < 0.001$], and bDMN-CER [$F(1, 70) = 14.1$, $p < 0.001$], but not for the other between network connections. The connectivity between the DMN and the other three networks was reduced in 0B versus rest (**Figure 3**). The significant network × genetic liability interaction reflected the fact that there was a significant effect of genetic liability for bFP-CER [$F(1, 70) = 13.9$, $p < 0.001$] and bCO-CER [$F(1, 70) = 15.2$, $p < 0.001$] connectivity, but not for the other between network connections. For both bFP-CER and bCO-CER, connectivity was overall lower in patients and their siblings compared to controls and their siblings (see **Figure 3**; Figure S5 in Supplementary Material).

WORKING MEMORY LOAD AND WITHIN-NETWORK CONNECTIVITY

The within-network ANOVA for working memory load again included genetic liability and family member type as between subject factors, and working memory load (0B, 1B, 2B) and network (wDMN, wFP, wCO, and wCER) as within subject factors. This ANOVA revealed a significant main effect of network [$F(3, 210) = 45.6$, $p < 0.001$] and a significant load × network interaction [$F(6, 420) = 6.39$, $p < 0.001$]. The main effect of genetic liability was not significant [$F(1, 70) = 0.07$, $p > 0.9$] and there were no significant interactions with genetic liability (all $ps > 0.15$). To determine the source of the load × network interaction, we computed separate ANOVAs for each of the four networks and employed FDR for multiple comparison correction. These ANOVAs revealed significant, but opposite effects, of load on connectivity within the DMN [$F(2, 140) = 13.4$, $p < 0.0001$] and FP [$F(2, 140) = 13.0$, $p < 0.0001$] networks. Connectivity decreased with increasing load within DMN, but increased with load within FP network (see **Figure 4**; Figure S6 in Supplementary Material). We should again note that while the network × load × genetic liability interaction was not significant, the follow-up contrasts did indicate a genetic liability × load interaction in wDMN connectivity [$F(2, 140) = 3.67$, $p = 0.028$]. This effect would not survive FDR correction for multiple comparisons, but did reflect the fact

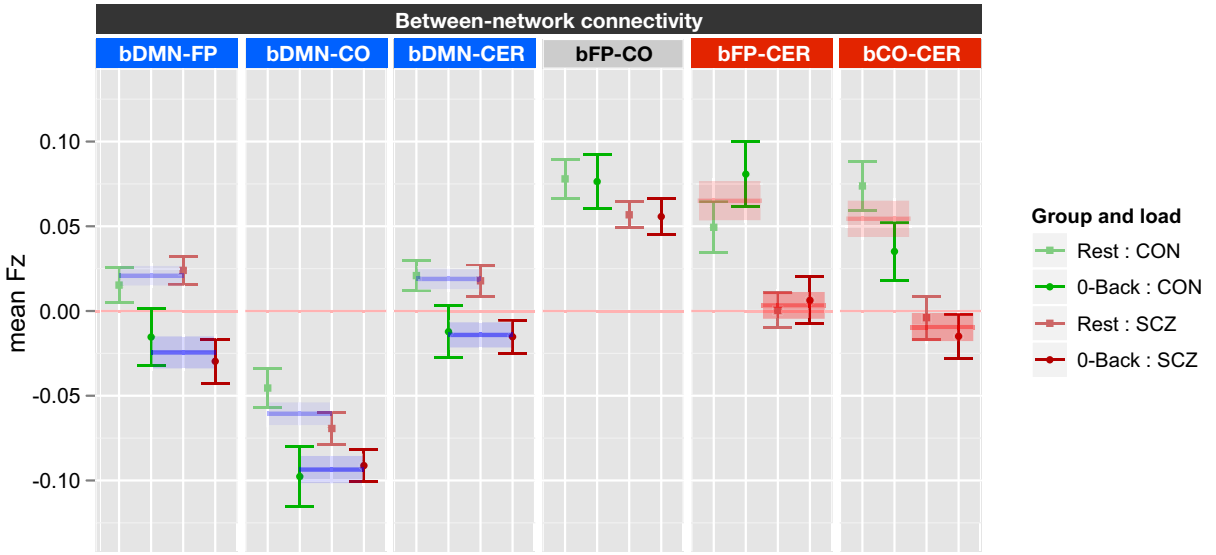

FIGURE 3 | Graph illustrating 0-back versus rest between network connectivity collapsed across siblings. SCZ, individuals with schizophrenia and siblings of individuals with schizophrenia; CON, healthy controls and siblings of healthy controls; DMN, Default Mode Network; FP, Frontal–Parietal Network; CO, Cingulo-Opercular Network; CER, Cerebellar Network; b, between. Segments marked in blue indicate networks which showed significant main effects of task (0-back versus rest). The main effect of task is further illustrated by blue lines and shading showing data collapsed across all groups (mean and standard error). Segments marked in red indicate networks that showed a significant main effect of genetic liability (SCZ versus CON). The main effect of genetic liability is further illustrated by red lines and shading showing data collapsed across task conditions (mean and standard error for each group across task and rest). See Figure S5 in Supplementary Material for data plotted for each of the four groups separately.

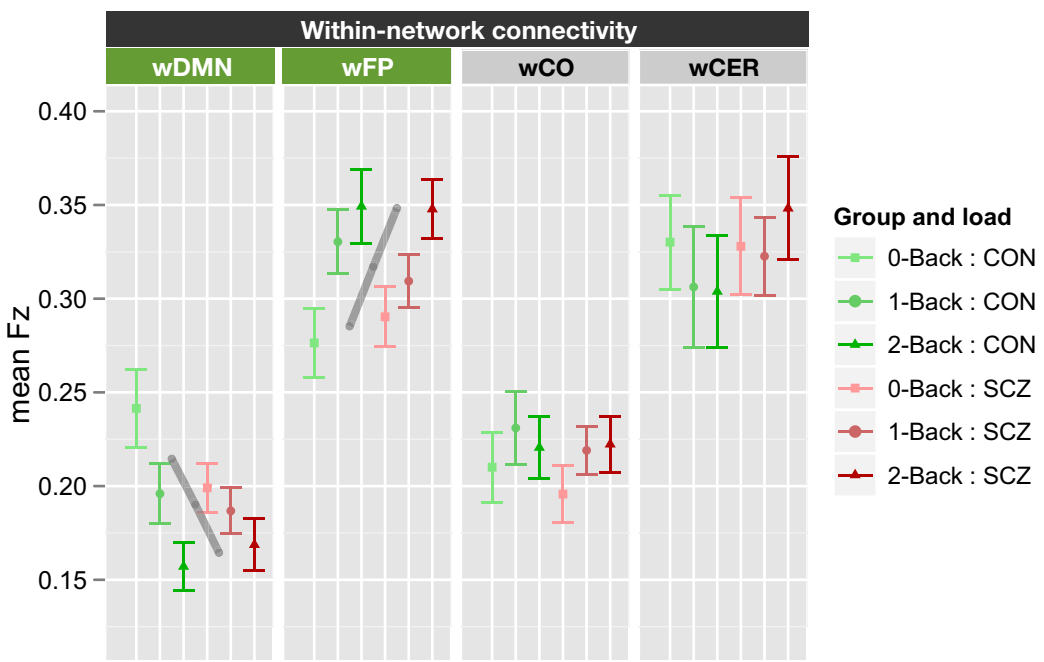

FIGURE 4 | Graph illustrating within-network connectivity as a function of working memory load collapsed across siblings. SCZ, individuals with schizophrenia and siblings of individuals with schizophrenia; CON, healthy controls and siblings of healthy controls; DMN, Default Mode Network; FP, Frontal–Parietal Network; CO, Cingulo-Opercular Network; CER, Cerebellar Network; w, within. Segments marked in green indicate networks that showed significant main effects of working memory load (0B, 1B, 2B) and the gray lines further illustrate the significant main effect of load across groups (mean across groups). See Figure S6 in Supplementary Material for data plotted for each of the four groups separately.

that the decrease in wDMN connectivity as a function of memory load was less in SCZ and SCZ-SIB than in CON and CON-SIB.

WORKING MEMORY LOAD AND BETWEEN NETWORK CONNECTIVITY

Finally, the effects of working memory load and genetic liability on between network connectivity was tested using the same ANOVA design as for within-network connectivity. The results revealed significant main effects of genetic liability [$F(1, 70) = 16.1$, $p < 0.001$], network [$F(5, 350) = 64.1$, $p < 0.001$], and working memory load [$F(2, 140) = 12.2$, $p < 0.001$]. In addition, the genetic liability × network [$F(5, 350) = 2.48$, $p = 0.031$] and working memory load × network [$F(10, 700) = 6.17$, $p < 0.001$] interactions were also significant. To examine the source of the working memory load × network interaction, we conducted separate ANOVAs for each of the six between network connections, using FDR to control for multiple comparisons. These analyses revealed significant effects of working memory load on bDMN-CO [$F(2, 140) = 7.9$, $p < 0.001$], bFP-CO [$F(2, 140) = 21.4$, $p < 0.0001$], and bFP-CER [$F(2, 140) = 7.93$, $p < 0.001$] connectivity, but not for the other between network connections. The significant genetic liability × network interaction reflected the fact that we also observed significant main effects of genetic liability for bFP-CER [$F(1, 70) = 14.1$, $p < 0.001$] and bCO-CER [$F(1, 70) = 8.78$, $p = 0.004$] connectivity, but not for the other between network connections. For both bFP-CER and bCO-CER, connectivity was overall lower in SCZ and their siblings compared to CON and their siblings (see **Figure 5**; Figure S7 in Supplementary Material). Importantly, however, these effects did not further interact with load. Thus, even though connectivity was overall lower for bFP-CER (which showed a main effect of working memory load) in SCZ and SCZ-SIB, SCZ, and SCZ-SIB still showed an increase in bFP-CER connectivity as load increased.

RELATIONSHIP TO CLINICAL AND COGNITIVE VARIABLES

In our previous work on resting state connectivity in this sample, we had found that bFP-CER connectivity (which was lower in SCZ and SCZ-SIB) predicted neuropsychological performance on IQ, working memory, episodic memory, and executive function assessed outside of the scanner. In addition, bFP-CER predicted disorganization symptoms. Thus, we wished to examine whether connectivity during task also predicted cognitive function, either on the working memory task performed in the scanner, or on the neuropsychological measures assessed outside of the scanner. We focused on the connectivity measures that differed between groups: bFP-CER, bFP-CO, and wDMN. For task connectivity, we examined the average connectivity across working memory loads, since none of the significant group differences interacted with load. We computed partial correlations between the connectivity measures and the cognitive and clinical measures, controlling for group status. Neither the resting state nor task connectivity measures for DMN displayed any significant correlations. However, as shown in **Table 2**, resting state bFP-CER connectivity again predicted better cognitive performance (working memory, episodic memory, and executive function) and fewer disorganization symptoms, though these are not new results given that this sample closely resembled the one in our prior study. As can be seen in Figure S9 in Supplementary Material, the relationship between bFP-CER and cognitive performance are consistent across groups. In contrast, as

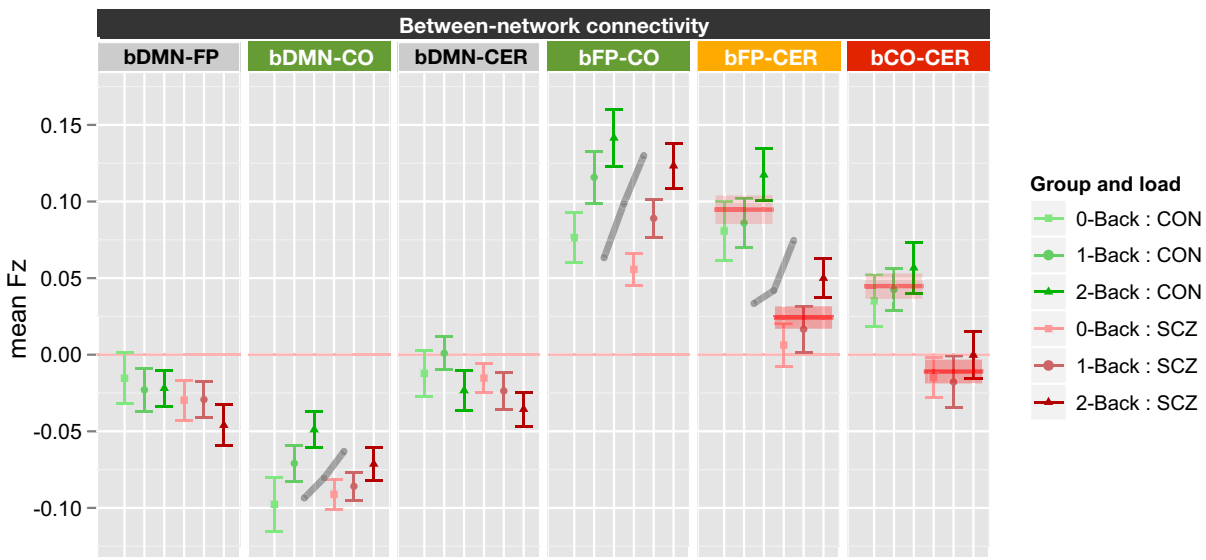

FIGURE 5 | Graph illustrating between network connectivity as a function of working memory load collapsed across siblings. SCZ, individuals with schizophrenia and siblings of individuals with schizophrenia; CON, healthy controls and siblings of healthy controls; DMN, Default Mode Network; FP, Frontal–Parietal Network; CO, Cingulo-Opercular Network; CER, Cerebellar Network; b, between. Segments marked in green indicate networks that showed significant main effects of working memory load (0B, 1B, 2B) and the gray lines further illustrate the significant main effect of load across groups (mean across groups). Segment marked in orange showed both a significant main effect of load and a significant main effect of genetic liability (SCZ versus CON). The segment marked red indicates the network that showed only a significant main effect of genetic liability (SCZ versus CON). The red lines further illustrate the statistically significant effects of genetic liability (mean and standard error for each group across memory loads). See Figure S7 in Supplementary Material for data plotted for each of the four groups separately.

Table 2 | Correlations between connectivity measures and cognitive and clinical variables.

	Connectivity type			
	Resting FP to CER connectivity	**Resting CO to CER connectivity**	**Task FP to CER connectivity**	**Task CO to CER connectivity**
***N*-BACK PERFORMANCE (*r*)**				
0-back	0.20	0.19	0.01	−0.32**
1-back	0.35**	0.25*	0.03	−0.16
2-back	0.22	0.20	0.09	−0.07
COGNITIVE DOMAINS				
IQ	0.18	0.24*	0.11	−0.03
Working memory	0.32**	0.19	0.28*	0.09
Episodic memory	0.33**	0.19	0.20	0.15
Executive function	0.34**	0.30*	0.17	0.04
CLINICAL DOMAINS				
Positive symptoms	0.01	−0.13	−0.09	−0.08
Negative symptoms	−0.20	−0.15	−0.07	−0.02
Disorganization	−0.26*	−0.25*	0.01	−0.08

*$p < 0.05$; **$p < 0.01$.

shown in Figure S10 in Supplementary Material the relationship between bFP-CER and disorganization symptoms is being driven by the SCZ, who have the most variance. Resting state bFP-CER (see Figure S8 in Supplementary Material) also predicted better performance on the *N*-back task (1-back accuracy), a result that was significant even among the SCZ and SCZ-SIB individually, but with similar trends in the CON and CON-SIB. In contrast, the task connectivity measures were not nearly so consistently associated with the cognitive variables, and were not associated with the clinical variables. Stronger task bFP-CER connectivity was not associated with better working memory performance. However, stronger task bCO-CER connectivity was actually associated with worse 0-back performance. We also present scatterplots for these correlations in Figures S8–S10 in Supplementary Material.

DISCUSSION

The goal of the current study was to examine the degree to which changes in functional connectivity in schizophrenia were dependent on the cognitive state of the individual (rest versus during working memory task performance) as a means to shed light on the potential mechanisms leading to altered functional connectivity in this illness. As a brief summary, we found that connectivity within the DMN and FP increased significantly between resting state and 0-back, while connectivity within the CO and CER decreased significantly between resting state and 0-back. Further, the DMN became significantly more "anti-correlated" with the FP, CO, and CER networks during 0-back as compared to rest. Additionally, we found that connectivity within both the DMN and FP was further modulated by memory load, and that connectivity between the FP and both CO and CER networks increased with memory load. Individuals with schizophrenia and their siblings showed consistent reductions in connectivity between both the FP and CO networks with the CER network, a finding that was similar in magnitude across rest and all levels of working memory load. The latter results are consistent with the hypothesis that functional connectivity changes associated with genetic liability to schizophrenia reflect stable alterations in brain connectivity that are not dependent on the state of the individual. We discuss each of these findings in more detail below.

CONNECTIVITY CHANGES AS A FUNCTION OF TASK STATE AND MEMORY LOAD

Consistent with prior work, we found that connectivity both within and between networks changed as a function of task state and working memory load (see **Figure 6** for a summary). Specifically, we found that connectivity within the FP increased during 0-back compared to rest, and continued to increase as a function of load. These findings are consistent with prior studies showing such connectivity increases among regions involved in the FP during working memory (Honey et al., 2002; Woodward et al., 2006; Ma et al., 2011; Nagel et al., 2011; Newton et al., 2011). The pattern of connectivity changes within the DMN was more complicated. Connectivity increased from rest to 0-back, generally consistent with the finding of Newton et al. (2011). However, connectivity then decreased again at 1-back, and even further at 2-back. Newton also found that DMN connectivity decreased at the highest working memory loads (though this was 3-back) and other researchers have found significant decreases in connectivity within the DMN during 2-back as compared to rest (Fransson, 2006). Thus, it is clear that DMN connectivity is modulated by task engagement and working memory load, but the exact pattern is more variable across studies than in the FP. In contrast to FP and DMN, connectivity within the CO and the CER networks decreased from rest to 0-back, but did not show any further load modulation. Such results suggest that connectivity within the CO and CER networks may dynamically reorganize as a function of overall task engagement, but not based on changes in difficulty within the task (e.g., load). This interpretation is broadly consistent with the suggestion that the CO network is involved in stable task set maintenance

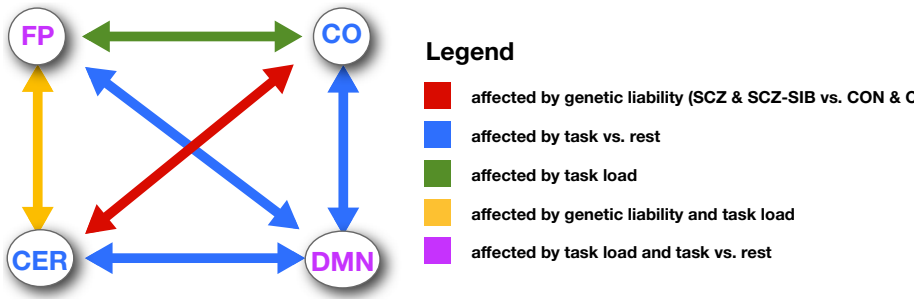

FIGURE 6 | Figure illustrating the pattern of changes in connectivity both within and between networks as a function of task state, memory load, and genetic liability.

(Dosenbach et al., 2006, 2007, 2008), while the FP may be more involved in dynamic modulation of task sets.

Interestingly, connectivity between the DMN and all three other networks became more negative in the 0-back conditions as compared to rest, and stayed stable across memory loads for DMN connectivity to FP and CER. However, DMN to CO connectivity became more similar to rest with increased memory load. The findings for DMN connectivity to FB and CER are consistent with prior work showing that at least parts of the DMN become more "anti-correlated" with the task-positive network during working memory performance (Leech et al., 2011). Further, such findings are consistent with the argument that effective task performance is associated with decreased activity in DMN regions as means of suppressing "off-task" cognitions (Shulman et al., 2003; Anticevic et al., 2010). However, other researchers have not always found significant increases in DMN anti-correlation with task-positive networks during task versus rest (Hampson et al., 2006; Newton et al., 2011), though this reflect power issues given the relatively small sample sizes in these prior studies.

Connectivity between the FP, CO, and CER networks did not change significantly between rest and 0-back. However, connectivity between the FP and both the CO and CER networks increased significantly as a function of memory load. The increased connectivity between FP and CO is consistent with several prior studies (Woodward et al., 2006; Nagel et al., 2011) and with the role of FP in dynamic task set modulation (Dosenbach et al., 2006). Further, it is consistent with the role of the CO in responding to errors and task conflict that may increase as a function of memory load (Botvinick et al., 2001, 2004). The increased connectivity between FP and CER as a function of memory load is also consistent with the fact that errors increase as a function of memory load, perhaps reflecting an enhanced need for error processing mechanisms supported by the CER (Ide and Li, 2011), which may signal the need for increased control provided by the FP network.

CONNECTIVITY CHANGES ASSOCIATED WITH GENETIC LIABILITY TO SCHIZOPHRENIA AS A FUNCTION OF TASK STATE AND MEMORY LOAD

We found very consistent evidence across task states and memory loads for altered connectivity in individuals with schizophrenia and their siblings, with reductions between the FP and CO networks and the CER network (see **Figure 6**). These connectivity reductions were present both at rest and across all working memory loads. The resting state findings are not new, and were the focus of a previous report (Repovs et al., 2011). However, the presence of similar changes in connectivity during working memory is a novel finding. Importantly, the magnitude of these connectivity reductions did not change as a function of task state. Further, individuals with schizophrenia and their siblings still showed significant increases in connectivity between FP and CER as a function of memory load, despite an overall reduction in connectivity. Additionally, the individuals with schizophrenia and their siblings also showed similar changes in connectivity between the FP and CO networks, as well as between the DMN and CO networks and within both the DMN and FP networks, as a function of memory load (though the genetic liability effects involving the DMN would not pass FDR correction). This pattern of results suggests two important things about the source of connectivity changes in schizophrenia. First, they suggest that these connectivity changes in schizophrenia patients and their siblings are unlikely to be due to confounding factors such as differences in what patients are thinking about during rest state scans, as the imposition of a structured task state did not alter the pattern of connectivity changes. Second, the fact that patients and their siblings showed a relatively intact ability to modulate connectivity as a function of task demands suggest that these connectivity changes are not simply the results of decreased task engagement. Instead, this pattern of results is more consistent with connectivity changes reflecting a more fundamental and/or trait like change in brain connectivity. Third, the fact that similar changes were seen in the individuals with schizophrenia and their siblings suggests that the results are likely more indicative of genetic liability to schizophrenia, rather than manifest disease itself. Functional connectivity is not isomorphic with structural connectivity (at least in terms of single synapse connections) and thus one cannot directly interpret alterations in function connectivity as reflecting alterations in structural connectivity. However, findings such as these point to the need to more directly examine the degree to which changes in functional connectivity are reflective of changes in white matter integrity and connections in schizophrenia. A growing number of studies have started to address this question, finding important initial evidence for overlap and interrelations between structural and functional connectivity changes in schizophrenia (Liu et al., 2008, 2011; Pomarol-Clotet et al., 2010; Camchong et al., 2011), and this is clearly an area ripe for additional research.

We also examined the relationship between individual differences in wDMN, bFP-CER, and bCO-CER connectivity and symptoms, neuropsychological performance and working memory task performance during fMRI scanning. Connectivity between CO and CER and connectivity within the DMN network did not predict cognitive performance or symptoms. However, as found in our prior work in this sample (Repovs et al., 2011), greater connectivity between the FP and CER networks predicted better performance on neuropsychological measures of working memory, episodic memory, and executive function, as well as fewer disorganization symptoms. Importantly, we also found that greater FP to CER connectivity predicted better accuracy on the *N*-back task (1-back condition) performed during fMRI scanning. Interestingly, however, these relationships were only significant for resting state connectivity and not for task connectivity. This was somewhat surprising to us, as we would have predicted greater relationships for task as compared to resting state connectivity. For the neuropsychological measures, the general patterns were the same for task and resting state connectivity, but this was not true for *N*-back performance or symptoms. Such findings could indicate that resting state data is a more sensitive indicator of functional connectivity changes relevant for cognitive performance and symptom manifestation, but such results need to be replicated in order to be confident in such an interpretation.

Of note, the primary analyses of within-network connectivity as a function of either task or memory load did not provide robust evidence for changes in individuals with schizophrenia or their siblings. However, the follow-up contrasts did reveal some evidence for altered connectivity within the DMN among individuals with schizophrenia, with less modulation of DMN as a function of task state and memory load. Although not robust, these findings are consistent with a number of other studies suggesting reduced DMN activity in schizophrenia during rest (Bluhm et al., 2007, 2009; Ongur et al., 2010; Rotarska-Jagiela et al., 2010; Camchong et al., 2011) and during task (Garrity et al., 2007; Kim et al., 2009a,b; Meda et al., 2009), though other studies have also found increased DMN activity in this illness (Whitfield-Gabrieli et al., 2009) or no differences in DMN connectivity (Woodward et al., 2011). These findings suggest that the exact patterns of DMN connectivity changes in schizophrenia are quite variable, and may be dependent both on task and sample characteristics, factors that need to be systematically examined in future studies.

It is of further interest to note that we found the most consistent connectivity changes in individuals with schizophrenia and their siblings in connections involving the CER, and the most consistent individual difference relationships were with the magnitude of connectivity between the FP and CER networks. These results are consistent with previous suggestions that cognitive impairments in schizophrenia reflect deficits in cortical–subcortical–cerebellar circuits (Andreasen et al., 1998; Andreasen and Pierson, 2008). There has been increasing interest in the cognitive and affective processing functions of the CER in recent years (Stoodley and Schmahmann, 2010; Koziol et al., 2011; O'Halloran et al., 2012), but it is not yet clear exactly how the CER contributes higher level cognition. One speculation is that the CER may play a key role in learning from errors, and in the timing and sequencing of a range of cognitive functions (Fiez et al., 1992; Fiez, 1996; Ravizza et al., 2006; Ben-Yehudah et al., 2007; Strick et al., 2009; Durisko and Fiez, 2010). Thus, disruptions in the coordination of CER activity with other networks may have major implications for impairments in cognitive adaptation and coordination, and may be relevant for understanding genetic liability to schizophrenia.

LIMITATIONS

There were several limitations in the current study. First, all of the individuals with schizophrenia were taking antipsychotic medication, and some prior research has suggested that medications may alter connectivity in schizophrenia (Lui et al., 2010). However, we found similar results in the siblings of individuals with schizophrenia, and none of the siblings were taking antipsychotic medications. This makes it unlikely that our primary findings were artifacts of medication status. Second, our prior study on resting state connectivity also found reductions in FP to CO connectivity among individuals with schizophrenia and their siblings. We did not find such changes in the current study, although the pattern was in the same direction in all conditions (lower connectivity in SCZ and SCZ-SIB). This could reflect the fact that some participants included in the prior study were not included in the current study, as they did not have task connectivity data. Alternatively, it could reflect the more stringent movement correction procedures implemented in the current study, based on the recently published work of Power and Petersen (Power et al., 2011). We also saw some trend level genetic liability effects involving the DMN, which did not pass FDR correction. It is possible this reflected power issues. With our sample size, we have 67% power to detect a medium effect size for the main effect of genetic liability in the task versus rest analysis, and 74% power in the working memory load analyses. At minimum however, our results suggest that the genetic liability effects on bFP-CER and bCO-CER connectivity changes were stronger than any such effects on connectivity involving DMN. One might also be concerned that including the siblings of individuals with schizophrenia and looking for main effects of genetic liability or interactions between genetic liability and family member type might have reduced power. To address this concern, we repeated all analyses with just the healthy controls and their siblings (treated as a single control group) and individuals with schizophrenia, excluding the siblings of the individuals with schizophrenia. As reported in the Supplementary Material, these analyses provided essentially identical results to the main analyses, suggesting that the inclusion of the siblings of individuals with schizophrenia did not mask any significant effects in the individuals with schizophrenia and that the inclusions of individual who shared some genetic relationship did not create spurious statistical results.

CONCLUSION

In summary, the current study provided robust evidence for reduced connectivity between the FP and CER networks and the CO and CER networks among individuals with schizophrenia and their siblings. These changes were present both at rest and during working memory task performance, and the magnitude of group differences in connectivity did not change as a function of task state or memory load. Such findings suggest that connectivity changes between networks involved in both

dynamic and stable task control and error processing in schizophrenia reflect fundamental changes in brain connectivity that are not secondary to task engagement or other state related factors, and which may reflect genetic liability to the illness. Further, changes in FP to CER connectivity predicted neuropsychological performance, symptoms, and *N*-back performance, though these relationships were stronger for resting state than task-based connectivity. These findings point to the need to examine the influence of changes in white matter integrity on alterations in functional connectivity, as a means to understand the causes of these robust changes in functional connectivity in schizophrenia that cut across task states and are present both in individuals with manifest illness and those genetically at risk for schizophrenia.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/Human_Neuroscience/10.3389/fnhum.2012.00137/abstract

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High classification accuracy for schizophrenia with rest and task fMRI data

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We present a novel method to extract classification features from functional magnetic resonance imaging (fMRI) data collected at rest or during the performance of a task. By combining a two-level feature identification scheme with kernel principal component analysis (KPCA) and Fisher's linear discriminant analysis (FLD), we achieve high classification rates in discriminating healthy controls from patients with schizophrenia. Experimental results using leave-one-out cross-validation show that features extracted from the default mode network (DMN) lead to a classification accuracy of over 90% in both data sets. Moreover, using a majority vote method that uses multiple features, we achieve a classification accuracy of 98% in auditory oddball (AOD) task and 93% in rest data. Several components, including DMN, temporal, and medial visual regions, are consistently present in the set of features that yield high classification accuracy. The features we have extracted thus show promise to be used as biomarkers for schizophrenia. Results also suggest that there may be different advantages to using resting fMRI data or task fMRI data.

Keywords: classification, fMRI, independent component analysis, KPCA, FLD

1. INTRODUCTION

Since the beginning of psychiatry, scientists have tried to develop methods for classifying patients with severe mental illness, in particular by examining differences between patient groups and healthy controls on neuroscientific measures. In this regard, neuroscientists have used event-related potentials (ERP) derived from the electroencephalogram (EEG) to characterize abnormalities in schizophrenia for over 50 years. One prominent ERP waveform that has held promise for differentiating schizophrenia from healthy controls is elicited by AOD stimuli (McCarley et al., 1991; Ford, 1999). However, these ERP studies have not proven to be sensitive enough to be used in classification or for diagnostic purposes.

Functional magnetic resonance imaging (fMRI) data, on the other hand, have been shown to have the potential to characterize and classify various brain disorders including schizophrenia with a higher degree of accuracy than other neuroimaging techniques such as ERPs (Levin et al., 1995; Calhoun et al., 2008b; Demirci et al., 2008). However, the high dimensionality (in terms of voxels) and noisy nature of fMRI data present numerous challenges to accurate analysis and interpretation. These challenges include choices for preprocessing, statistical analysis, feature selection, classification, and validation. Independent component analysis (ICA) is useful for fMRI analysis in extracting components to be used as powerful multivariate features for classification (McKeown et al., 1998; Calhoun et al., 2008a; Arribas et al., 2010). Spatial ICA decomposes fMRI data into a product of a set of time courses and independent components (ICs). Most ICs are reported to be identified consistently in healthy controls and schizophrenia patients (Calhoun et al., 2008a). However, some brain regions within these ICs show different activation levels in these two groups. To remove the redundancy and retain the most discriminative activation patterns from ICs, it is important to find an effective feature selection and extraction scheme.

Numerous research efforts have used fMRI activation levels to discriminate healthy controls and schizophrenia patients. Shinkareva et al. (2006) identified groups of voxels showing between-group temporal dissimilarity and worked directly with fMRI time series from those voxels for classification purposes, achieving a prediction accuracy of 86% using a leave-one-out cross-validation on 14 subjects (7 patients and 7 controls). In their classification approach, the task-associated stimulus was used to calculate the temporal dissimilarity matrix. However, in rest data, no such stimulus is presented and the data are not task-related. Thus, this approach is not applicable for such cases. Ford et al. (2002) combined structural and functional MRI data for classification purposes, proposing to use principal component analysis (PCA) to project the high dimensional data onto a lower dimensional space for the training set. The prediction accuracy of the classifier was tested in 23 subjects (15 patients and 8 controls) with a leave-one-out method, achieving a maximum classification accuracy of 87%. Since fMRI data tend to be smoothed and

clustered, there may exist higher-order correlations among voxels (Li et al., 2007). However, PCA is a linear transformation that projects the data to a new coordinate system such that the new set of variables are linear functions of the original ones, which can be achieved by eigenvalue decomposition of a data covariance matrix (Pearson, 1901; Hotelling, 1933). As a second-order method, PCA cannot take higher-order statistical information into account to discriminate healthy control from schizophrenia subjects.

In this paper, we propose a new approach to discriminate the above groups, using components estimated by ICA. The training and test data are processed completely separately in the procedure to avoid "double dipping" (Kriegeskorte et al., 2009). After obtaining ICs, we develop a three-phase feature selection and extraction framework as follows. First, a two-level feature identification scheme is performed to select significantly activated and discriminative voxels. Second, kernel PCA (KPCA) is used to extract non-linear features from the selected significant voxels by taking higher-order statistics into account. Then, Fisher's linear discriminant analysis (FLD) is performed to further extract features that maximize the ratio of between-class and within-class variability. This feature extraction framework is applied to two data sets, one collected during rest and the second during the performance of an auditory oddball task (AOD) acquired from the same set of healthy controls and schizophrenia patients. We evaluate the classification performance using individual and combined components as features. By performing a leave-one-out approach in each data set, we show that features extracted from several components such as default mode (DMN) and motor-temporal networks lead to a classification accuracy of over 90%. We find that features extracted from combined components produce a classification accuracy of 98% for AOD data and 93% for rest data. Several components, including DMN, temporal, and medial visual regions, are consistently contained in those combined components for both data sets. In our study, controls and patients are better discriminated when performing a task, although both data sets work well. Results also suggest that discriminative features are spread through a wide variety of intrinsic networks and not limited to one specific brain region or regions. The features extracted using our method show promise as potential biomarkers for schizophrenia.

The rest of this paper is organized as follows. We first briefly describe the two data sets and the preprocessing method. Next, we introduce the three-phase feature selection and extraction framework for the classification including a two-level feature identification scheme, KPCA and FLD. In Section 4, we present the experimental results and discuss them in Section 5, with conclusions presented in the last section.

2. DATA AND PREPROCESSING

2.1. DATA SETS

We analyze the fMRI data from 28 healthy controls and 28 chronic schizophrenia patients, all of whom provided IOI/Hartford Hospital and Yale University IRB-approved written, informed, consent. All participants were scanned during two runs of an AOD task and one 5 min run while resting, resulting in two AOD and one rest data sets per subject. The AOD task consisted of detecting an infrequent sound within a series of regular and different sounds. Auditory stimuli were presented to each participant by a computer stimulus presentation system via insert earphones embedded within 30-dB sound attenuating MR compatible headphones. The task had three kinds of sounds: target (1000 Hz with a probability of 0.10), novel (non-repeating random digital noises with a probability of 0.10), and standard (500 Hz with a probability of 0.80). Participants were instructed to respond as quickly and accurately as possible with their right index finger when they heard the target stimulus and not to respond to other sounds. Participants separately performed a 5-min resting-state scan (rest) where they were instructed to rest quietly without falling asleep with their eyes open while focused on an asterisk. An MRI compatible fiber-optic response device (Lightwave Medical, Vancouver, BC, Canada) was used to acquire behavioral responses. Preprocessing, including realignment, normalization, and smoothing, was performed in SPM5 (2011). Further details of the AOD paradigm and image acquisition parameters for both AOD and rest are described in Calhoun et al. (2008a), Kiehl et al. (2005). Patients were slightly older than controls. All but four patients and one control were right handed. Twenty-one patients were receiving stable treatment with atypical antipsychotic medications and nine patients were on antidepressants. Medication information was not available for seven patients. All patients in our study had chronic schizophrenia and symptoms were also assessed by positive and negative syndrome scale (PANSS). Demographic and clinical characteristics are reported in **Table 1**.

2.2. ICA ALGORITHM

The ICA analysis of fMRI data start with the spatial ICA model where $\mathbf{X} = \mathbf{AS}$, $\mathbf{S} = [\mathbf{s}_1, \ldots, \mathbf{s}_N]^T$ is an N-by-V source matrix, N is the number of sources, V is the number of voxels and $\mathbf{s}_i$ is the ith spatial component. The mixing matrix $\mathbf{A}$ is an M-by-N matrix

Table 1 | Demographic and clinical characteristics of patients with schizophrenia ($n = 28$) and healthy controls ($n = 28$).

Variable	SZ	HC	t/P-value
Age	39.4 ± 12.7	31.5 ± 11.1	2.4/0.02
Percent male	82	68	NS
NART, estimated IQ	105.3 ± 6.9	111.3 ± 8.3	NS
PANSS (P/N)	$15.8 \pm 5.5/15.4 \pm 5.6$	NA	NA
Percent treated with atypical antipsychotic medication	100	NA	NA
Percent treated with antidepressants	43	NA	NA
Percent with some psychotic symptoms	67	NA	NA

SZ, schizophrenia; HC, healthy control; NS, non-significant; NART, national adult reading test; NA, non-applicable; P/N, positive/negative; Group comparisons are reported in the last column.

where each column $\mathbf{a}_i$ represents the time course for the ith source. The goal of the ICA algorithm is to determine a demixing matrix $\mathbf{W}$ such that the sources are estimated using $\hat{\mathbf{S}} = \mathbf{WX}$ under the assumption of statistical independence of spatial components.

The sources of interest in fMRI data are commonly assumed to have a super-Gaussian distribution (Calhoun and Adali, 2006). The standard version of Infomax assuming such distribution sources produces consistent ICs (Correa et al., 2007; Du et al., 2011). It minimizes the mutual information among the estimated sources by maximizing information transfer from the input to the output within a network through a non-linear function (Bell and Sejnowski, 1995). Hence, we apply Infomax in our fMRI analysis. Instead of entering each subject's data into a separate ICA analysis, we use a group ICA (Calhoun et al., 2001; Erhardt et al., 2011) technique implemented in the Group ICA of fMRI Toolbox (GIFT, 2011) to estimate a set of spatial components.

In the ICA step, ICs belonging to several brain networks are generated. Our classification approach includes the extraction of powerful features from those ICs. The advantage of using ICA is to evaluate the classification power with different networks. Hence, the ICA step is important and necessary in the classification method we presented.

2.3. CLASSIFICATION PREPROCESSING

The classification procedure uses a leave-one-out method to evaluate performance of the feature extraction framework. For each left-out test subject, the remaining 55 subjects (including controls and patients) comprise the training set. In order to avoid the bias introduced by processing the training and test data together, we perform group ICA each time to decompose the training data. The single-subject spatial maps for the test data are obtained using back-reconstruction via regression, also called spatial-temporal regression (STR; Erhardt et al., 2011).

Group ICA consists of two dimension reduction stages. At the subject level, the number of components for each subject is first reduced to 40 by PCA; the reduced components from each subject are then concatenated. At the group level, the number of components for the aggregate group is reduced to 30. This order has proven to be consistently estimated for fMRI data sets from two AOD sessions and one resting-state session (Li et al., 2011). We then perform ICA on this final set. Since the ICA algorithm is iterative, we use ICASSO (Himberg and Hyvarinen, 2003) in GIFT to improve robustness of the estimated results. ICASSO runs the ICA algorithm several times, producing different estimated components for each run and then collects the components by clustering them based on the absolute value of the correlation between source estimates (Himberg and Hyvarinen, 2003). Reliable estimates correspond to tight clusters including components that have high correlations with each other. We perform ten runs with different initial values on 30 clusters, which latter is the same as the number of estimated components. Instead of using the average of different runs, we select the centrotype of the cluster for each component as the best estimate. Then, for each session of each subject in the training set, spatial components, and time courses are obtained from the back-reconstruction step.

To obtain spatial components for the test subject, we use the ICA model $\mathbf{X} = \mathbf{AS}$ as the STR model. First, time courses of the test subject are calculated by $\mathbf{A}_t = \mathbf{X}_t\mathbf{S}_g^{\dagger}$, where $\mathbf{X}_t$ is the observation matrix of the test subject, $\mathbf{S}_g$ is the aggregate results estimated from the training group and each column of $\mathbf{A}_t$ corresponds to the time course of the test subject. Then spatial components of the test subject are calculated by $\mathbf{S}_t = \mathbf{A}_t^{\dagger}\mathbf{X}_t$. Next, we calculate the mean of spatial components in the training set and convert it to Z-values. The definition of Z-value is $Z = (s-\mu)/\sigma$, where s is the value of each voxel, μ is the mean of all voxels, and σ is the standard deviation. To generate a mask containing only binary values, we set the values of voxels in the Z-map to be 1 if $|Z| > 0.5$, otherwise to be 0, then apply this mask to the spatial component obtained from STR to generate a better defined component for later analysis.

The same preprocessing procedure used in the training and test data is then applied to the rest and AOD data set. All spatial components are converted to Z-values. Hence, the image intensities provide a relative strength of the degree to which a particular component contributes to the data, thus enabling us to compare spatial components across different subjects (Calhoun et al., 2001; Allen et al., 2011; Erhardt et al., 2011). Since we have two AOD and one rest data set per subject, we average spatial components of two AOD data sets and convert them to Z-values.

As our data consist of 56 subjects, we perform group ICA 56 times on different training sets and obtain corresponding spatial components of each test subject using STR. However, group ICA introduces a permutation ambiguity. We need to generate several masks to select the same component from each training set. To simplify the problem, we use components obtained from group ICA to generate masks, and then calculate correlations between each spatial component and a particular mask in different training sets. The component providing the largest correlation value corresponds to the same brain region as the mask. Using these procedures, 14 components of interest were selected from 30 ICs based on visual inspection and were correlated with corresponding components in each training set. The 14 components of interest were advanced to the next step.

3. METHODS

The feature extraction method for the classification consists of three steps: a two-level feature identification scheme, kernel PCA, and Fisher's linear discriminant analysis, as illustrated in **Figure 1**. First, we generate a two-level feature identification scheme to select significant features based on statistical hypothesis testing such as t-tests. Second, we perform KPCA to compute low dimensional representations of the significant features selected in the first step. KPCA computes the higher-order statistics without the combinatorial explosion of time and memory complexity (Schölkopf et al., 1998). Then we apply FLD to further extract features that maximize the ratio of between- and within-class variability.

The kernel Fisher discriminant analysis (KFD) combines the kernel trick with FLD (Mika et al., 1999; Baudat and Anouar, 2000). The KFD always encounters the ill-posed problem in its real-world applications and with KPCA and FLD together, we could make full use of two kinds of methods and achieve a more powerful discriminator (Yang et al., 2005). Our algorithm applies a two-phase KFD using KPCA and FLD together.

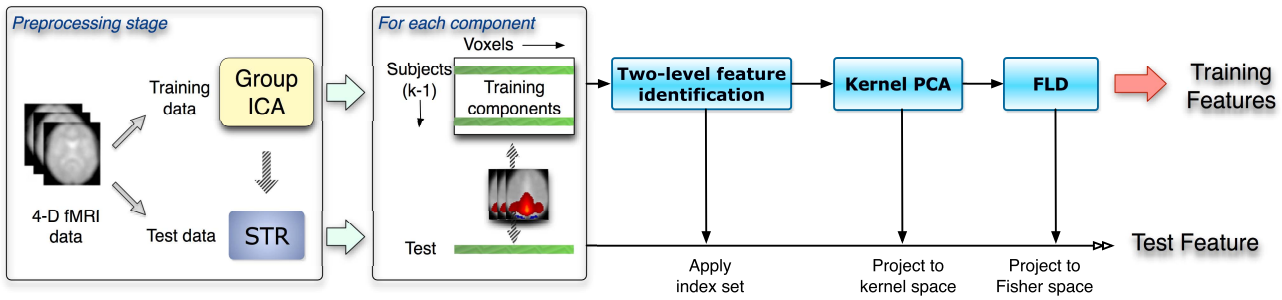

FIGURE 1 | The flow chart shows a leave-one-out scheme given *k* subjects. This includes the preprocessing stage and the three-phase feature selection and extraction framework. Spatial components as inputs are obtained from the data preprocessing stage. Training and test data are processed separately in the whole procedure.

3.1. TWO-LEVEL FEATURE IDENTIFICATION

FMRI data are high dimensional in terms of numerous voxels and have high noise levels. Even though we select only a small number of ICs after ICA, each IC still contains more than 60 k voxels, which may provoke over-fitting in a classifier without prior dimension reduction. In order to avoid the "curse of dimensionality" and select significant voxels, we apply one-sample and two-sample t-tests to the selected components.

T-tests are among the most widely used statistical significance measures currently adopted in feature selection. The one-sample t-test is used to infer whether an unknown population mean differs from a hypothesized value. For instance, we have training data $x_1, \ldots, x_n$ assumed to be independent realizations. Then we test the following hypothesis:

$$\text{Null Hypothesis} : H_0 : \mu = \mu_0$$
$$\text{Alternate Hypothesis} : H_1 : \mu \neq \mu_0.$$

The mean is estimated by the sample mean $\bar{x}$. The greater the deviation between $\bar{x}$ and μ_0, the greater the evidence that the hypothesis is untrue. The test statistic t is a function of this deviation, standardized by the standard error of $\bar{x}$. It is defined as

$$t = \frac{\bar{x} - \mu_0}{\sigma / \sqrt{n}}.$$

We compute voxel-wise one-sample t-tests separately for the control and patient groups in the training set, which treats each subject as a random effect and provides a statistical threshold on the components. The null hypothesis is set to be H_0: $\mu = 0$ and the test statistic is treated as the threshold in selecting significant features. The thresholds are the same for both groups and defined as t_1. Voxel positions are recorded in an index set if the t-values are larger than the threshold t_1. Then we obtain a union index set of significantly activated voxels in both control and patient groups.

Next, we compute a voxel-wise two-sample t-test between the two groups, using a two-sample t-test to assess whether the means of the two classes are statistically different from each other by calculating a ratio between the difference of two class means and the variability of the two classes. The training data are selected from

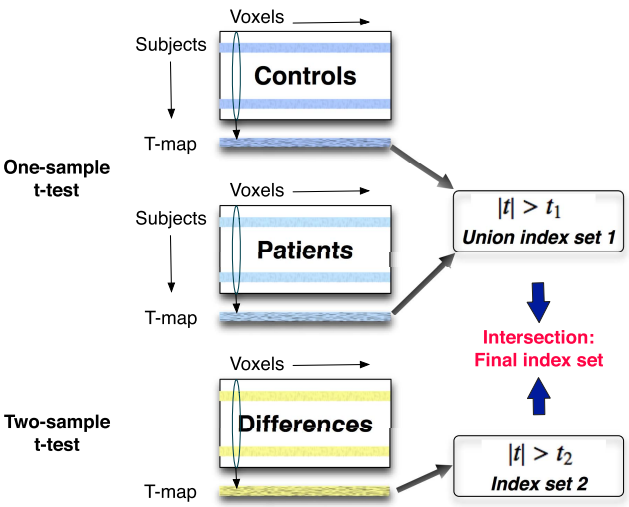

FIGURE 2 | A one-sample *t*-test is applied across the same components separately to the control and patient groups in the training set. A two-sample t-test is performed to find voxels that are significantly different between two groups. The features including the significantly activated and different voxels are identified in this two-level feature identification scheme.

two groups, $x_{11}, \ldots, x_{1n_1}$ and $x_{21}, \ldots, x_{2n_2}$, and it is desired to test the null hypothesis $\mu_1 = \mu_2$ (Dalgaard, 2008). The test statistic is defined as

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\sigma_1^2 / n_1 + \sigma_2^2 / n_2}}.$$

The threshold of two-sample t-test is denoted as t_2. An index set of significantly different voxels is composed of the voxel positions where two-sample t-statistics are larger than t_2. Next, we calculate the intersection of index sets obtained from one-sample and two-sample t-test to generate a final index set with significant positions in the training set. Then we apply this final index set to components of interest for the test set to select significant voxels. The scheme of the two-level feature identification is shown in **Figure 2**.

3.2. KERNEL PCA

After the two-level feature identification step, the dimension of features is reduced to thousands (this value depends on t-test thresholds), which, however, is still high to some classifiers. Moreover, in fMRI, activation patterns of BOLD-related sources tend to be spatially smoothed and clustered. These contextual features encoded in the signal sample space are not exploited in a standard ICA framework (Li et al., 2007). Thus, higher-order correlations may exist among voxels. To reduce feature dimensions and take higher-order statistics into account, we apply KPCA to project the input data into a new space using a non-linear mapping and apply linear PCA in this new space.

For a given non-linear mapping $\mathbf{\Phi}$, the input data space $\mathbf{R}^n$ can be mapped into a new space called feature space F (Schölkopf et al., 1998):

$$\mathbf{\Phi} : \mathbf{R}^n \to F$$
$$\mathbf{x} = (x_1, \ldots, x_n) \mapsto \mathbf{\Phi}(\mathbf{x}) = (\Phi_1(\mathbf{x}), \ldots, \Phi_N(\mathbf{x})).$$

The mapping can lead to a potentially much higher dimensional feature vector in the feature space F. The additional feature dimensions which indicate the complexity of the function class matters can be useful for performing target classification (Müller et al., 2001). KPCA, as described in (Schölkopf et al., 1998; Müller et al., 2001), is shown as follows.

First, given a set of training samples $\mathbf{x}_k$, $k = 1, \ldots, M$, $\mathbf{x}_k \in \mathbf{R}^n$, we define an $M \times M$ matrix $\tilde{\mathbf{K}}$ with entries $k(\mathbf{x}_i, \mathbf{x}_j)$, where

$$k(\mathbf{x}_i, \mathbf{x}_j) = \langle \mathbf{\Phi}(\mathbf{x}_i), \mathbf{\Phi}(\mathbf{x}_j) \rangle$$

is the kernel representation. We obtain centered data $\mathbf{\Phi}(\mathbf{x})$ by centralizing $\tilde{\mathbf{K}}$, such that

$$\mathbf{K} = \tilde{\mathbf{K}} - \mathbf{1}_M\tilde{\mathbf{K}} - \tilde{\mathbf{K}}\mathbf{1}_M + \mathbf{1}_M\tilde{\mathbf{K}}\mathbf{1}_M,$$

where the matrix $\mathbf{1}_M$ is the M-by-M matrix with all entries equal to $1/M$.

Second, we compute the eigenvectors of $\mathbf{K}$ and normalize them in feature space by

$$\beta^j = \frac{1}{\sqrt{\lambda_j}}\mathbf{K}\alpha^j, j = 1, \ldots, m,$$

where m is the dimension after KPCA, $\lambda_1 > \lambda_2 > \ldots > \lambda_m$ denote the m largest positive eigenvalues of the kernel matrix $\mathbf{K}$, $\alpha^1, \ldots, \alpha^m$ are the corresponding eigenvectors, and $\beta^1, \ldots, \beta^m$ are the normalized eigenvectors in feature space.

Third, for a training sample $\mathbf{x}_k$, we can obtain the KPCA transformed feature vector $\mathbf{y}_k = [y_{k1}, y_{k2}, \ldots, y_{km}]^T$ by $\mathbf{y}_k = \langle \mathbf{V}, \mathbf{\Phi}(\mathbf{x}_k) \rangle$, where $\mathbf{V}$ is a matrix of eigenvectors in feature space and specifically,

$$y_{kj} = \sum_{l=1}^{M} \beta_l^j k(\mathbf{x}_l, \mathbf{x}_k), j = 1, \ldots, m. \quad (1)$$

For a test data $\mathbf{x}_i$ with a mapping $\mathbf{\Phi}(\mathbf{x}_i)$ in feature space, we project the data onto the subspace generated by the training data. Then the KPCA transformed feature vector $\mathbf{y}_i = [y_{i1}, y_{i2}, \ldots, y_{im}]^T$ is obtained by (1).

In summary, the following steps are necessary to compute the features for training and test data (Schölkopf et al., 1998): (1) compute the matrix $\mathbf{K}$ using all training data, (2) compute its eigenvectors and normalize them in feature space F, and (3) compute projections of training and test data onto the eigenvectors.

Algorithm 1 classifier based on euclidean distance
Require: features of training data and test data as inputs, such that f_i, $i = 1, 2, \ldots, 55$, and f_t

1. **Calculate** $d_i = ||f_t - f_i||_2$, $d^{[c]} = \frac{1}{n_1}\Sigma_{i=1}^{n_1} d_i^{[c]}$, and $d^{[p]} = \frac{1}{n_2}\Sigma_{i=1}^{n_2} d_i^{[p]}$
2. **if** $d^{[c]} < d^{[p]}$ **then**
3. the test data belongs to the control group
4. **else**
5. the test data belongs to the patient group
6. **end if**
7. **return** the class label of the test subject

Algorithm 2 feature combination algorithm
Require: for a test subject, input component matrix $\mathbf{X}_i$, $i = 1,2, \ldots, m$ and $\mathbf{X}_i = (\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_{56})^T$

1. given an initial value $num = 0$ and calculate the majority value $M = m/2 + 1$ or $M = (m+1)/2$
2. **for** $k = 1 \to m$ **do**
3. $\mathbf{f}_k = \mathcal{F}(\mathbf{X}_k)$
4. classify the test subject using Algorithm 1
5. **if** the test data is classified into the control group **then**
6. $num \leftarrow num + 1$
7. **end if**
8. **end for**
9. **if** $num \geq M$ **then**
10. the test data belongs to the control group
11. **else**
12. the test data belongs to the patient group
13. **end if**
14. **return** the class label of the test subject

3.3. FLD

The Fisher discriminant function aims to achieve an optimal linear dimensionality reduction, by employing a linear projection of the data onto a one-dimensional space, such that an input vector $\mathbf{x}$ is projected onto $y = \mathbf{w}^T\boldsymbol{x}$, where $\mathbf{w}$ is a vector of adjustable weight parameters (Fisher, 1936; Bishop, 1995). In general, the projection onto one dimension leads to a considerable loss of information. However, by adjusting $\mathbf{w}$, we can achieve a projection that maximizes the class separation and also does not lose within-class compactness. The resolution proposed by Fisher is to maximize a function representing the difference between the projected class means, normalized by a measure of the within-class scatter along the direction of $\mathbf{w}$. The Fisher criterion is given by

$$J(\mathbf{w}) = \frac{\mathbf{w}^T\mathbf{S}_B\mathbf{w}}{\mathbf{w}^T\mathbf{S}_w\mathbf{w}}, \quad (2)$$

where $\mathbf{S}_B$ is the between-class covariance matrix and is given by

$$\mathbf{S}_B = (\mathbf{m}_2 - \mathbf{m}_1)(\mathbf{m}_2 - \mathbf{m}_1)^T$$

and $\mathbf{S}_W$ is the total within-class covariance matrix, given by

$$\mathbf{S}_W = \sum_{n\in C_1} (\mathbf{x}^n - \mathbf{m}_1)(\mathbf{x}^n - \mathbf{m}_1)^T + \sum_{n\in C_2} (\mathbf{x}^n - \mathbf{m}_2)(\mathbf{x}^n - \mathbf{m}_2)^T.$$

The mean vectors of the two groups are given by

$$\mathbf{m}_1 = \frac{1}{n_1}\sum_{n\in C_1} \mathbf{x}^n \text{ and } \mathbf{m}_2 = \frac{1}{n_2}\sum_{n\in C_2} \mathbf{x}^n,$$

where n_1 and n_2 are the numbers of controls and patients in the training set. The objective $J(\mathbf{w})$ is maximized by $\mathbf{w} \propto \mathbf{S}_W^{-1}(\mathbf{m}_2 - \mathbf{m}_1)$, where $\mathbf{w}$ is the eigenvector corresponding to the largest eigenvalue of $\mathbf{S}_W^{-1}\mathbf{S}_B$.

3.4. PARAMETERS AND CLASSIFIER

For different thresholds in the two-level identification scheme, the proposed feature extraction framework generates different features for the training data. In order to obtain a set of features characterized by sufficiently large discrimination power, we select a combination of thresholds t_1 and t_2 that maximizes the value of the objective function $J(\mathbf{w})$ shown in (2) in the training stage. Then the selected thresholds are applied to all data, including training and test data. After obtaining significant features, we calculate the Euclidean distances between the test feature and all training features, such that $d_1^{[c]}, \ldots, d_{n_1}^{[c]}, d_1^{[p]}, \ldots, d_{n_2}^{[p]}$, where c denotes the healthy control and p the patient group. By comparing the mean distances between the test data and each training group, we classify the test data into the closest group. The classifier algorithm is labeled and described as Algorithm 1.

4. EXPERIMENTAL RESULTS

In our experiments, the AOD and rest data sets are used to evaluate the performance of the proposed feature extraction method. We select 14 components of interest as features to discriminate healthy controls and patients in each data set. The components are labeled as follows and the t-maps for these components are shown in **Figure 3**: (1) DMN, (2) temporal, (3) motor-temporal, (4) sensorimotor, (5) anterior DMN (medial frontal), (6) anterior frontal, (7) lateral frontal, (8) fronto-insula, (9) motor, (10) posterior parietal, (11) right frontoparietal, (12) left frontoparietal, (13) cerebellum, and (14) medial visual components.

We first use individual components of interest as inputs of the feature extraction framework. Then a leave-one-out approach is performed to validate the classification procedure. Second, we combine features in a majority vote method to classify the left-out test subject. We show the accuracy, sensitivity, and specificity of the obtained classification results. Accuracy is calculated as the ratio between the number of test data sets classified into the correct group and the total number of test data sets. Sensitivity and specificity are defined and calculated as shown in **Table 2**.

Table 2 | The definitions of sensitivity and specificity.

	Condition	
Test outcome	True positive (TP)	False positive (FP)
	False negative (FN)	True negative (TN)
	Sensitivity = TP/(TP + FN)	Specificity = TN/(FP + TN)

TP, correctly diagnosed patients; FP, incorrectly identified patients; TN, correctly diagnosed controls; FN, incorrectly identified controls.

During the training stage, we repeat the process of the two-level feature identification, KPCA and FLD to calculate the value of the objective function in (2) for each combination of thresholds. If the thresholds are selected as large values, a few voxels are retained after the two-level feature identification step. To reduce the computation time and retain more information, we use the values of 0–3 with the increment of 0.5 for t_1 in the one-sample t-test and the same interval for t_2 in the two-sample t-test. We select the combination of thresholds leading to the maximum value of (2) in this range. To implement KPCA, we use the polynomial kernel function primarily due to its simplicity as it has a simpler structure and by selecting different orders, we can control the degree of non-linear mapping. It is defined as

$$k(\mathbf{x},\mathbf{y}) = \left(\mathbf{x}^T\mathbf{y} + 1\right)^d,$$

where d is the order of the polynomial kernel. Also, our experimental results show that the polynomial kernel function performs better than the Gaussian kernel in KPCA in our task when tested with a number of kernel widths. For the polynomial kernel, we use $d = 3$ in our experiments. The dimensionality of the underlying KPCA space cannot be allowed to exceed $M - c$, where M is the total number of training samples available and c is the number of classes (Martínez and Kak, 2001). In our study, $M = 55$, $c = 2$. Thus, we set the dimension of principal components after KPCA to 53. **Figure 4** shows visualization of features for controls versus patients after each feature extraction step. Results show that training samples are linearly separable after the three-phase feature extraction.

4.1. CLASSIFICATION USING AOD DATA

4.1.1. *Classification using individual component*

Components selected from ICA results are independent brain images, each of which can be considered as an independent feature vector and used as the input of our feature extraction framework. We find 14 components of interest in our AOD data. As shown in **Figure 1**, after the training stage, a significant feature is extracted from one component for each subject. Then we use a simple classifier given in Algorithm 1 to discriminate the test data. Classification results are shown in **Table 3**.

4.1.2. *Classification using combined features*

Since each component of interest may provide different information in discriminating healthy controls and patients, we also wanted to evaluate results when incorporating more than one component. We select m components from the 14 components of interest and input them into $\mathcal{F}$, denoting the feature extraction framework shown in **Figure 1**. Then for each test subject, we

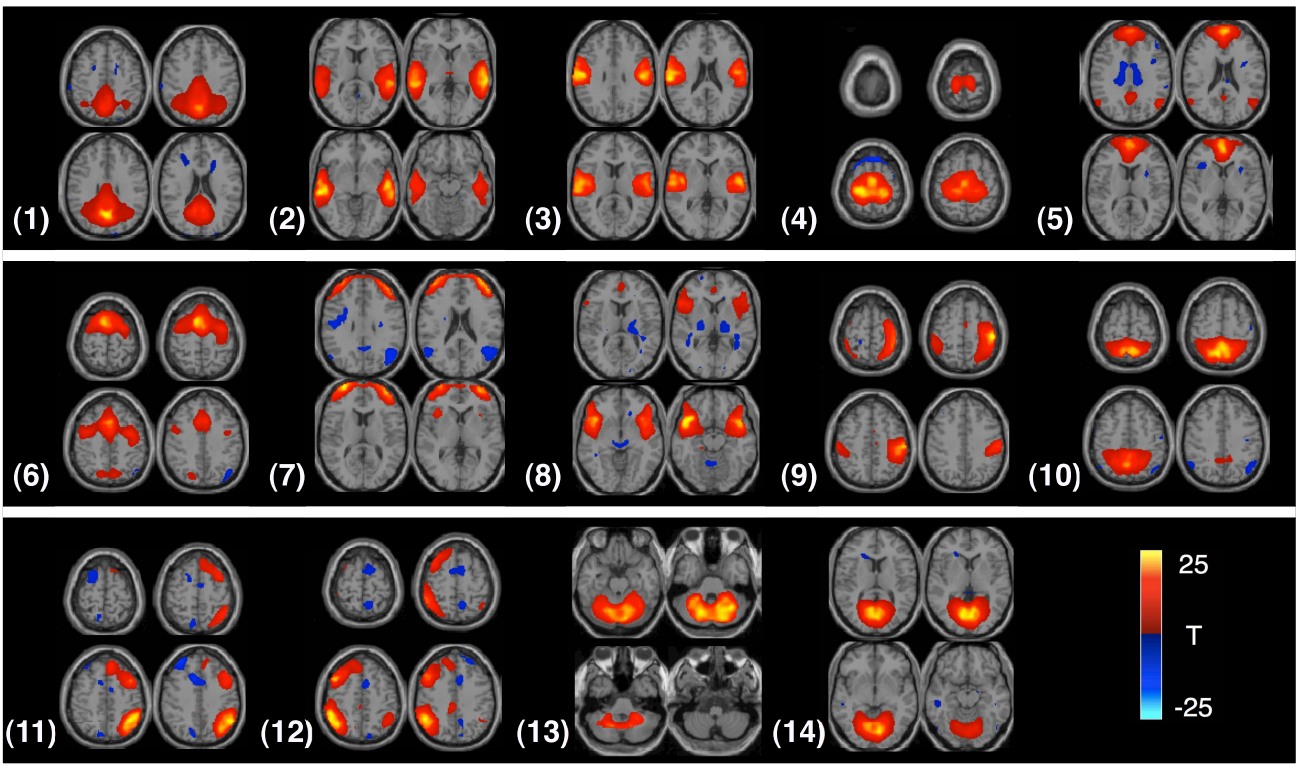

FIGURE 3 | Four slices from each component are shown in the figure; components are identified from the AOD task. Each component is entered into a one-sample *t*-test and thresholded at $P < 1e{-}7$ (corrected for multiple comparisons using the family wise error (FWE) approach, implemented in SPM5).

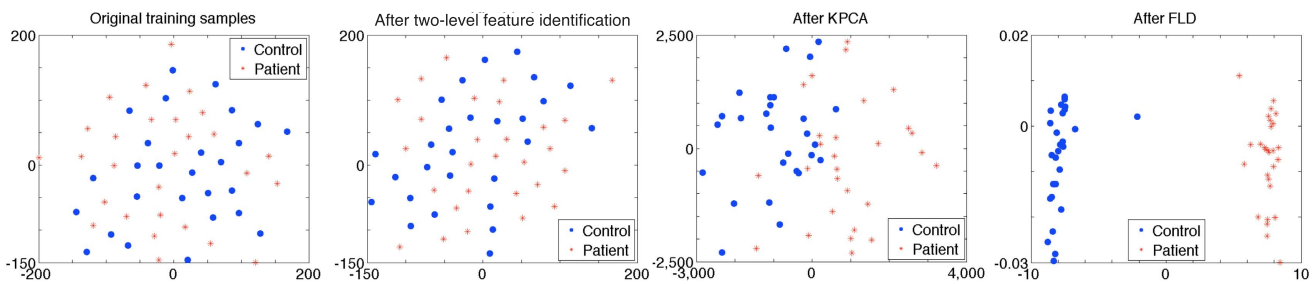

FIGURE 4 | The figure shows features for controls versus patients after each feature extraction step. Each dot represents an individual and the color of the dot indicates the correct diagnosis of either control (blue) or schizophrenia (red). Individuals are close to each other if the Euclidean distances between training data are small. The original training samples cannot be separated by a linear classifier. A two-level feature identification step is used to select significantly different voxels. After KPCA, most of training samples separate to two groups. Training samples are linearly separable and a maximum margin is obtained after FLD. Parameters in two-level feature identification step are $t_1 = 0.5$ and $t_2 = 0.5$, which are selected during the training stage using the DMN component (from rest data) as input to the framework.

use classification results obtained from *m* components to provide a vote and classify the test subject into the group based on the majority vote. If more than half of selected components classify the test data into the control group, then the test subject is assigned to the control group, otherwise the test subject is assigned to the patient group. The algorithm for combining features is labeled and described as Algorithm 2. In our experiments, we explore all possible combinations of the 14 components of interest to discriminate the test data. The component combinations leading to the highest accuracy is shown in **Table 5**.

4.2. CLASSIFICATION USING REST DATA

4.2.1. Classification using individual component

In the rest data, we select components of interest as same as those in AOD data. We select 13 components of interest from ICA results, corresponding to those obtained above, with the exception of the

Table 3 | Classification results with AOD data (one component as features).

Index	Accuracy	Sensitivity	Specificity
1	0.93	0.93	0.93
2	0.86	0.89	0.82
3	0.91	0.86	0.96
4	0.88	0.86	0.89
5	0.82	0.82	0.82
6	0.86	0.86	0.86
7	0.84	0.75	0.93
8	0.84	0.89	0.79
9	0.82	0.79	0.86
10	0.80	0.82	0.79
11	0.79	0.71	0.86
12	0.82	0.86	0.79
13	0.84	0.68	1.00
14	0.86	0.79	0.93

Table 4 | Classification results with rest data (one component as features).

Index	Accuracy	Sensitivity	Specificity
1	0.91	0.89	0.93
2	0.88	0.86	0.89
3	NA	NA	NA
4	0.84	0.86	0.82
5	0.82	0.93	0.71
6	0.80	0.82	0.79
7	0.82	0.79	0.86
8	0.84	0.82	0.86
9	0.84	0.89	0.79
10	0.79	0.79	0.79
11	0.80	0.82	0.79
12	0.82	0.82	0.82
13	0.80	0.64	0.96
14	0.84	0.89	0.79

motor-temporal component. This latter component could be estimated in the control group, but it could not be consistently derived from the patient group. Thus, we exclude the motor-temporal component in the classification of rest data. We extract features using the proposed framework from these 13 ICs and classify the test data; results are shown in **Table 4**.

4.2.2. Classification using combined features

The feature combination method in Algorithm 2 is used in the rest data set. Since the motor-temporal component is not included in the experiment, the component with index 3 is not used in the feature combination. We assess every combination of the 13 components to discriminate the test data and then evaluate classification performance. Several combinations lead to similar classification results; some of those with the highest accuracy are shown in **Table 5**.

Table 5 | Classification results using feature combination.

Data set	Combinations	Sensitivity	Specificity	Accuracy
AOD	1, 2, 3, 8, 14	0.98	1.00	0.98
Rest	1, 2, 11	0.93	0.93	0.93
	1, 4, 14			
	1, 2, 4, 11, 14			

5. DISCUSSION

5.1. DURING AOD TASK AND AT REST

In this paper, we propose a novel method for effective feature selection and extraction. We evaluate the performance of several components of interest extracted as features using our method by discriminating healthy controls from schizophrenia patients during an AOD task and at rest. Our results show that features extracted from the DMN and the motor-temporal component lead to significantly high classification accuracy, providing additional support to previous studies, which noted the importance of these components for discriminating patients with various mental diseases from controls (Calhoun et al., 2008b; Sui et al., 2009). We also find that components leading to the highest classification accuracy, including DMN, temporal, and medial visual regions, are consistently included among the combined components for both data sets, since similar components have been observed for participants during an AOD task and at rest (Calhoun et al., 2008a). Overall, the AOD task appears to be more discriminating across more components than the resting fMRI data as shown in **Figure 5**.

The DMN is one of the most widely analyzed networks derived from resting-state fMRI data. It is commonly observed to deactivate during task-based fMRI experiments proportionately to task difficulty (McKiernan et al., 2003). This network shows significant activity differences between controls and schizophrenia patients (Garrity et al., 2007), although in most such comparisons, including the current analysis, patients are taking antipsychotic medications, which themselves affect DMN activity (Lui et al., 2010) and may thus exaggerate patient/control differences. In our classification results shown in **Tables 3** and **4**, the discrimination accuracy is highest using features extracted from DMN for both data sets. Moreover, classification accuracy is slightly higher for AOD than rest data. In DMN, activity decreases are consistent across a wide variety of task conditions (Raichle and Snyder, 2007; Raichle, 2010). Consequently, there are more patient/control DMN differences during the AOD task than at rest.

Other regions important for diagnostic discrimination include temporal and motor areas. The temporal region is involved in auditory processing and motor areas are responsible for the perception and execution of actions. Since participants were asked to press a button when they heard the target sound in the AOD task, brain regions related to auditory and motor functions are expected to be highly activated. Two components related to auditory function are derived from AOD data, one designated the temporal and the other the motor-temporal component. Researchers in several fields postulate important links between auditory and motor areas (Hickok et al., 2003). In our results, using the motor-temporal

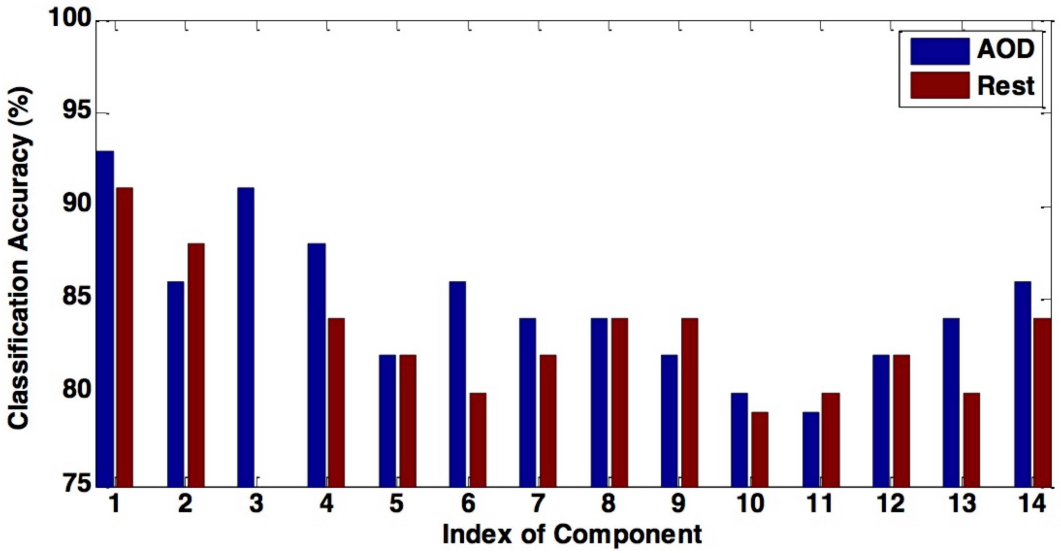

FIGURE 5 | The figure shows the comparison between the classification accuracy in AOD and rest data. Using most of components of interest can lead to a higher accuracy in the AOD data than the rest data.

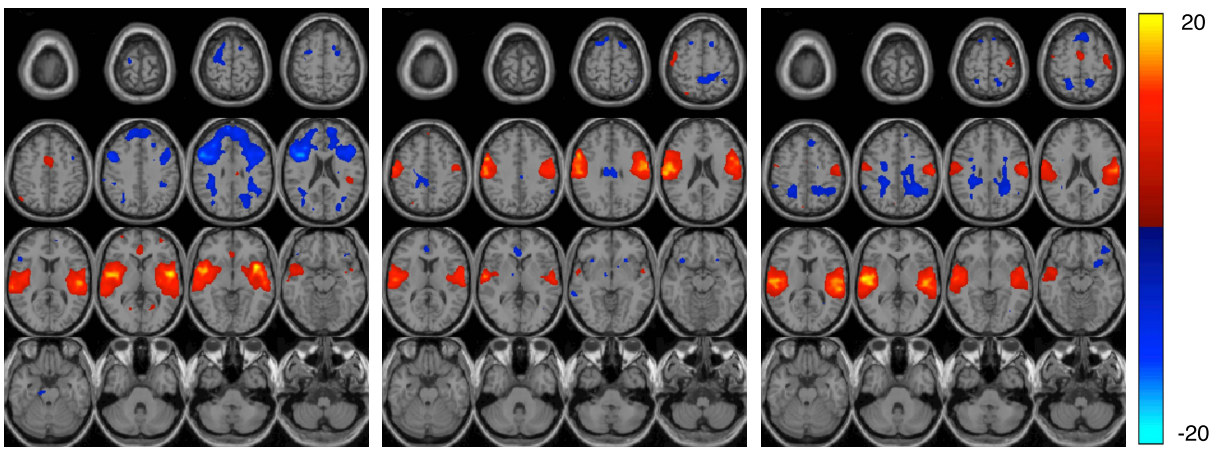

FIGURE 6 | The figure shows three estimated components in the rest data set. Each component is entered into a one-sample *t*-test and thresholded at $P < 0.01$ (corrected for multiple comparisons using FWE) shown with 16 slices. The left and middle components are the estimated temporal and motor-temporal components in the control group, respectively. The right component is the only temporal related component estimated in patients.

component as a classification feature reveals a high accuracy in discriminating controls and patients in the AOD task. Conversely, in the rest data, the motor-temporal component could not be consistently estimated in patients but was obvious in the control group. The temporal and motor-temporal components are clearly separated in the control group at rest but not so in patients. This is shown in **Figure 6**. This suggests that the auditory-motor link is weaker in schizophrenia than in healthy controls. The motor-temporal component can be directly estimated in the patient group during the AOD task, since participants are instructed to press a button when they hear the target sound; this condition forces the motor-temporal component to be estimated. Our numerical results in **Table 4** show that using the temporal component as a feature leads to a higher accuracy for rest compared to AOD data. Since patients may lose attention and/or perform poorly during a task, using other motor-related components (such as sensorimotor, anterior frontal, and cerebellum) in AOD data also lead to a high accuracy in our results.

The feature combination data reveal that a combination of DMN, temporal, motor-temporal, fronto-insula, and medial visual components results in the highest classification accuracy for AOD data. These five components are task-negative networks. In the rest data, several combinations of components result in the highest accuracy. These components, including DMN, temporal, and medial visual regions, are consistently included among those

combined components for both data sets. The fronto-insula component is often recruited by cognitively demanding tasks and frequently interpreted as a part of a task-related activation network (Seeley et al., 2007). Thus, the fronto-insula component might be expected to have more significant effect in discriminating groups in AOD data, derived from performance of an actual task, than in rest data.

5.2. MOTION ARTIFACTS

Motion artifacts are common causes of image degradation in fMRI, and patients are more prone to exhibit body movements during scanning procedures for a variety of reasons. Hence, motion artifacts may amplify differences between controls and patients in classification results. Our fMRI data are preprocessed in SPM (Friston et al., 1995; SPM5, 2011) to minimize movement artifacts. In the preprocessing procedure, a set of realignment parameters reflecting the relative orientations of the data is saved for each subject. To evaluate the influence of motion artifacts in our classification results, we then use these realignment parameters as features to perform another classification.

In processing the AOD data set, we average realignment parameters from the two sessions per participant resulting in a 249×6 matrix for each subject (249 time points, each of which has 6 parameters). Similarly, in the rest data set, a 204×6 matrix is obtained for each subject (from 204 time points in these data). We use a leave-one-out cross-validation and the same classifier in Algorithm 1 to evaluate the classification results. To certify the result, we extract several kinds of features from the realignment parameters to perform the same classification. For each subject, the feature vector comprises the mean value of parameters of each time point. Another approach is to use feature vectors consisting of the maximum value of parameters of each time point, or the feature vector comprises mean (or maximum) values across all time points. In addition, we can select mean (or maximum) values of the parameter matrix for each subject as the feature. For the AOD data, the accuracy of using realignment parameters as features is from 48 to 54% and for the rest data, the accuracy is from 34 to 52%. Therefore, motion artifacts appear to have little impact on our classification results.

5.3. MULTIPLE SESSIONS IN AOD DATA

Our analysis used two runs of AOD task data and one session of rest data. For a representative comparison, we also use the first session of AOD data in the same analysis. The results are almost the same as previous and remain the same when we combine features in a majority vote method. The most likely reason for these results is that we treat two sessions of data as two different subjects in the group ICA analysis, first doubling the number of subjects in AOD data. We then average the components from the two sessions as the input of our classification framework. This procedure has few effects on our classification results.

5.4. AVOID "DOUBLE DIPPING" IN THE ANALYSIS

Double dipping, the use of the same data set for selection and selective analysis, provides distorted descriptive statistics and invalid statistical inference whenever the resulting statistics are not inherently independent of the selection criteria under the null hypothesis (Kriegeskorte et al., 2009). In our classification, including the step that ICs of training data are selected by group ICA and ICs of the left-out test data are generated by spatial-temporal regression, initially separates the training and test data. Then, we use only training data to select thresholds in the two-level feature identification scheme and generate feature spaces in Kernel PCA and Fisher's linear discriminant analysis. The left-out test feature is obtained by applying selected thresholds to ICs and projecting selected voxels to the training feature space. For different training sets and corresponding left-out test subjects, the classification procedures are independent. Thus, the problem of using the same data set both to train and to test classification is completely avoided in our method.

5.5. VALIDATION OF THREE-PHASE FEATURE EXTRACTION

In order to see whether all three steps were essential, we eliminated the first step and performed KPCA and FLD directly on all voxels. This two-step approach resulted in significant performance loss. For example, features extracted from DMN component, without the first step, lead to a classification accuracy of 73%, which is significantly lower than the current result shown in Section 4. Those unselected voxels in the first step are more likely to be noise and do not provide sufficient information to discriminate patients from healthy controls. Hence, the three-phase feature extraction framework is meaningful and necessary in the classification method we have presented.

6. CONCLUSION

We introduce a three-phase feature extraction framework that takes higher-order statistics into account and satisfies the Fisher's criterion, with components of interest estimated from ICA algorithm as inputs. Three steps of the framework include a two-level feature identification scheme, KPCA, and FLD. First, a two-level feature identification scheme is performed to select significantly activated and discriminative voxels from components of interest. Second, KPCA is used to extract non-linear features from the selected significant voxels by taking into account higher-order statistics. Then, FLD is performed to further extract features that maximize the ratio of between- and within-class variability. Experimental results using both AOD and rest data are included to demonstrate the performance of the proposed framework. Results show that features extracted from DMN and motor-temporal components lead to significantly high classification accuracies. Moreover, we implement a majority vote method to incorporate different components of interest into combined features. Several components, including DMN, temporal, and medial visual regions, are consistently contained in the combined components leading to the best classification accuracy for both data sets. By comparing the classification results from AOD and rest data, we find significant interactions and differences between these data sets for several components of interest. One possible limitation of the present work is that all patients were on psychotropic medication during the testing. It is possible that the medication effects could artificially enhance our classification results. However, the obtained high classification accuracy, combined with the fact that several networks all have powerful ability to distinguish patients from controls, suggests that this is not a

dominant effect. Another possible limitation is the small number of subjects used in the current study. Hence, it is desirable to determine to what degree the medication impacts functional classification and it is desirable to extend the database to include more subjects. However, features extracted using the method we presented show very promising results in terms of classification performance and it is reasonable to say that the framework can be applied to extract significant features from components of interest that can be used to discriminate patients from healthy controls.

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