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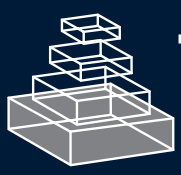
AN UPDATE ON NEUROCOGNITIVE IMPAIRMENT IN SCHIZOPHRENIA AND DEPRESSION

Hosted by
Kenneth Hugdahl and Vince D. Calhoun



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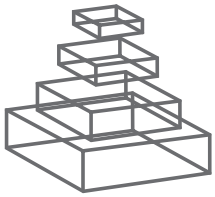

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AN UPDATE ON NEUROCOGNITIVE IMPAIRMENT IN SCHIZOPHRENIA AND DEPRESSION

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Despite all research that has been devoted to schizophrenia over the last years, the understanding of the biological bases of the disorder is still fragmentary. Adding to the complexity is the realization that basic cognitive functions are seriously distorted, and that removal of symptoms does not necessarily ameliorate the cognitive deficits. It has also been shown that cognitive deficits can occur before clinical symptoms, in a prodromal phase of the disorder, pointing to a possible causal relationship between cognitive deficits and outbreak of the disorder. However, it is still not possible to diagnose a patient from cognitive deficits alone, or from a combination of clinical symptoms and cognitive deficits, and structural and functional neuroimaging data, although promising, have also not found the way to routine clinical practice. The aim of the Research Topic is therefore to provide an update on research on cognitive and brain imaging research for the understanding of cognitive deficits in schizophrenia. The suggested contributors are all internationally recognized experts in their respective fields. The suggested contributions will cover the field from the use of standardized neuropsychological tests to establish cognitive response profiles in patients with schizophrenia to the use of advanced new techniques for the analysis of brain imaging data.

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EDITORIAL
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An update on neurocognitive impairment in schizophrenia and depression

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Despite the considerable research that has been devoted to schizophrenia and depression over the last years, the understanding of the biological bases of these disabling disorders is still fragmentary. Adoption-, twin- and family studies, provide clear evidence of strong genetic components to these mental disorders, although multiple loci are likely to be involved. The effect of pharmacological intervention has hinted at specific neurotransmitter systems of etiological importance, but the lack of receptor specificity of therapeutic drugs have thwarted any simple linkage of behavioural and molecular phenotypes. More recently brain imaging investigations, like PET and functional magnetic resonance imaging (fMRI), have identified candidate structural and functional abnormalities, including work in identifying changes in networks of brain regions, but these findings are still preliminary and need to be integrated with other accumulating knowledge.

Of particular interest in the last decade that is adding to the complexity of the picture, is the realization that basic cognitive functions are seriously distorted, and that removal of core symptoms such as paranoia and hallucinations does not necessarily ameliorate the cognitive deficits. It has also been shown that cognitive deficits can occur before clinical symptoms in schizophrenia, in a prodromal phase of the disorder, pointing to a possible causal relationship between cognitive deficits and outbreak of the disorder. Similarly, it has been reported that removing clinical symptoms in depression does not alleviate cognitive symptoms, like impaired concentration and focus of attention. However, it is still not possible to diagnose a patient from cognitive deficits alone, or from a combination of clinical symptoms and cognitive deficits, and structural and functional neuroimaging data, although promising, have also not found the way to routine clinical practice.

The aim of the current special topic is to provide an update on research on cognitive and brain imaging research for the understanding of cognitive deficits in these disorders, with a focus on recent developments in structural and functional neuroimaging, including recent advances in tracking of white matter fibres, and electroencephalography (EEG) and novel computational measures.

Vince Calhoun et al. show how fMRI can be used not only to identifying regions where hemodynamic response amplitudes can differentiate between patient and control groups, but also how such amplitude based comparisons can estimate temporal correlations and compute maps of functional connectivity between regions. In their article, Calhoun et al. review work related to how these brain networks are pervasive also in a relaxed resting state, included the default mode network and how such analysis can provide novel approaches to yielding biomarkers for schizophrenia and other mental disorders, which can be described both in terms of disrupted local processing as well as altered global connectivity between large scale cortical networks. The paper also introduces new statistical approaches to functional connectivity, emphasizing the use of independent component analysis.

Bjørn Rishovd Rund reviews recent research and discusses whether schizophrenia is a neurodegenerative disorder, with progressive neuronal degeneration as the illness progresses. Acknowledging that this issue has been discussed ever since the identification of schizophrenia as a disorder of its own, Rund focuses on what can be learned from recent cognitive and brain imaging data. He takes the position that although there are reports of cognitive decline the longer the patient has been ill, and corresponding grey matter changes, there is no convincing evidence of a progressive neurodegenerative process after onset of illness. He further posits that MRI and cognitive changes can be explained by reference to compensatory mechanisms and cognitive reserve theory after the onset of schizophrenia, at the same time as cognitive functioning does not get increasingly impaired in the course of the disorder.

Dara Manoach and Robert Stickgold raises the often neglected and poorly understood issue of sleep disorders in schizophrenia and ask the important question if abnormal sleep impair memory consolidation in schizophrenia? Starting with the observation that sleep abnormality often impairs cognitive functioning in healthy individuals it is imperative to delineate whether a similar relationship exists in mental disorders where cognition is affected. Manoach and Stickgold suggests that the evolution of memory consolidation over time is facilitated by sleep, and they then review existing data that abnormal sleep in schizophrenia disrupts attention and impairs sleep-dependent memory consolidation and task automation. The authors conclude that these sleep-dependent impairments may contribute substantially to the generalized cognitive deficits in schizophrenia and that focus on the amelioration of sleep disturbances may have important consequences for clinical improvement.

Åsa Hammar and Guro Årdal review their work on cognitive function in patients with major depression, and the question if repeated relapses of depressed episodes increasingly impair cognition and if cognition is similarly restored after symptom treatment and restoration of normal functioning. Hammar and Årdal review recent research that has focused on cognitive functioning in the severe phase of depression, where it is widely accepted that the disease is characterized by cognitive impairment in the acute state.

They then go on to review their own work that has used an experimental approach focusing on attention shift and attentive search processes. They show that cognitive impairment remains during depressed episodes despite clinical improvement. The authors also show that impaired ability to perform the attention tasks employed in their studies is related to frequency of depressed episodes and with the duration of episodes.

Else-Marie Løberg and Kenneth Hugdahl review available studies on a relationship between cannabis use and cognitive functioning in schizophrenia. It is an established fact that cannabis use is quite frequent in schizophrenia. It has also been suggested that cannabis actually can be a contributing causal factor in schizophrenia, which may interact with the typical neurocognitive vulnerability seen in this patient group. Løberg and Hugdahl reviews the literature and of the 23 studies that were found, a clear majority reported either improved cognitive functioning or no change, with only one study reporting a decline. These paradoxical findings may be explained by several alternative hypotheses. One hypothesis is that the cannabis group overall has a better functioning with superior social skills, enabling drug acquisition. Another hypothesis is that cannabis use could have a positive influence on brain functioning, but taking the negative effects of cannabis on brain and psychosis into account, this is not probable. A cannabis-related schizophrenia group study show poorer prognosis and studies on premorbid functioning are inconclusive. The authors speculate that cannabis may, through a breakdown of brain function, imitate the typical neurocognitive vulnerability seen in schizophrenia.

Jazmin Camchong et al. present two studies from their laboratory where they have used diffusion tensor MR imaging (DTI) to obtain brain anatomical connectivity information in patients with schizophrenia and healthy controls by examining the directional organization of white matter microstructure. The authors use DTI to address the important question of whether brain connectivity and its abnormalities may be heritable traits associated with schizophrenia. The first study investigated if healthy monozygotic (MZ) twin pairs and random pairings among twins would show different correlations with regard to DTI measures of neuronal connectivity. The results showed that there was a stronger correlation between MZ twin pairs than between randomly generated pairs in several regions in the brain critically involved in cognitive function. In a second study the same approach was applied to first-degree relatives of schizophrenia patients and a healthy control group. The results showed that relatives of schizophrenia patients had reduced connectivity in brain regions involved in controlling higher cognitive functions. The authors suggest that a DTI connectivity approach may be a valuable approach to unravelling new endophenotypes in schizophrenia.

Kevin Spencer provides data from a neuro-computational approach to elucidate the question of functional consequences of cortical circuit abnormalities on gamma oscillations in schizophrenia. In particular Spencer uses a computational model of cortical circuitry to examine the effects that neural circuit abnormalities might have on EEG gamma frequency generation and network excitability. The results showed that reducing synaptic connectivity (e.g. NMDA receptor input) had a negative effect on gamma frequency power and phase synchrony. Reducing neuronal spiking activity output impaired gamma generation to a lesser degree than reducing synaptic connectivity, thereby increasing network excitability. It is suggested that a neuro-computation approach, combining non-invasive neurophysiological and structural measures, might be able to distinguish between different neural circuit abnormalities in schizophrenia patients. Computational modelling may help to bridge the gaps between post-mortem studies, animal models, and experimental data in humans, and facilitate the development of new therapies for schizophrenia and neuropsychiatric disorders in general.

Godfrey Pearlson and Vince Calhoun ask why endophenotypes are important in schizophrenia, and suggest a distinction between definitions of endophenotypes versus biomarkers and the implications of this for the understanding of neurocognitive deficits. A starting point for their discussion is that because the pathophysiology of schizophrenia is obscure, there is no laboratory test or biological marker deriving from the core etiopathology that can be reliably used in diagnosis and treatment outcome evaluation. Pearlson and Calhoun then review existing data on the relationship between abnormal brain functioning and cognitive functioning, focusing on activation in the dorsolateral prefrontal cortex and adjacent regions and working memory, an often implied endophenotype. The authors identifies several problems with current approaches to the study of endophenotypes, such as patients not understanding the tasks, or task fatigue, and suggest alternative approaches such as simpler experimental tasks that might avoid difficult to interprate floor effects. They also advocate the use of resting state and default mode network paradigms, applying independent component analysis techniques to reveal functional networks rather than isolated brain regions when searching for endophenotypes and biological markers of schizophrenia.

Emma Thomas and Rebecca Elliott review work related to recent research on the neural basis of cognition in depression, focusing on the distinction between emotional and non-emotional processing. Cognitive deficits are among the core deficits in depression and also listed in recent diagnostic manuals as core symptoms, in particular reduced concentration and poor memory. Another equally important class of cognitive processes is the investigation of mechanisms of emotional disturbance, such as negative bias of thoughts and excessive response to failure. The article reviews the major emotional and non-emotional cognitive processes in depression, together with findings from neuroimaging studies. They conclude on the basis of their review of the data that models of cognitive dysfunction in depression is underscored by disrupted cortico-limbic circuitry, and discuss how connectivity analysis MRI techniques can be used to test such models explicitly, revealing important clinical implications of cognitive imaging in depression. Understanding of such relationships may have important consequences for diagnosis and treatment of depression and depressive episodes.

Matcheri Keshavan and colleagues review previous work on premorbid cognitive deficits and their relationship to brain structure in young relatives of schizophrenia patients. They note cognitive deficits in the adolescent population which also manifest in first-degree relatives. The primary deficits include psychomotor speed, memory, attention, reasoning, and social-cognition in addition to generalized measures such as intelligence. Of note, the age of adolescence may be a useful "window" for observing premorbid

impairments in neurocognition. They also examine the relationship between brain structure and cognitive measures. There is much evidence of neurocognitive deficits, but more study is needed to improve our understanding of their structural underpinnings. In addition the potential to use these measures as biomarkers and possibly endophenotypes should be explored further.

Daniel Mathalon and colleagues present a study of electrophysiological abnormalities in schizophrenia and schizoaffective disorder (SA). In particular, P300 differences including amplitude and latency have been widely studied in schizophrenia but have not been well studies in SA. Interestingly they found that although P300 amplitude was preserved in the SA group the latency and reaction times were affected similarly in schizophrenia and schizoaffective disorder. These changes could not be accounted for by other measured demographic variables and suggests that the underlying pathophysiology of the two groups is different.

Sophia Frangou provides a selective review of cognitive function in early onset schizophrenia. Changes in IQ, attention, executive function and memory have been observed and in this group, which provides a unique way to study the trajectory of the disease in a more severe variant of adult onset schizophrenia. Frangou identified a consistent pattern of abnormalities in the various cognitive domains. In addition to finding evidence that the cognitive profile of the early onset group was similar to that of the less severe adult onset group she highlighted age related improvements which existed for healthy adolescents but not for patients.

Leighton Hinkley and colleagues present a magnetoencephalography (MEG) study of the neural connectivity in schizophrenia patients. They present several approaches for maximizing the sensitivity of the MEG technique including adaptive spatial filtering, different functional connectivity metrics, and study the relationship to various cognitive and clinical outcomes. The use of MEG can be used to augment existing work by adaptive existing paradigms used in EEG and fMRI to MEG. Finally they discuss experimental paradigms which demonstrate important utility in relating impaired connectivity to characteristic findings in schizophrenia.

In summary, the current collection of articles represents the wide range of topics related to cognitive impairment in schizophrenia and depression. In this respect the special topic issue provides compelling evidence that cognitive impairment is a primary aspect of both schizophrenia and depression, and not secondary to other symptoms and disease processes. The current selection of articles also show how recent developments in structural and functional neuroimaging, including both hemodynamic and electrophysiology, may further advance our understanding of how cognition is impaired in these disorders. The more complete picture of these disorders provided by cognitive measures, neuroimaging, and also genetics will likely be important tools in future diagnostics and treatment evaluation.

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Cognitive function in early onset schizophrenia: a selective review

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Schizophrenia is widely regarded as the clinical outcome of aberrant neurodevelopment caused by a combination of genetic and non-genetic factors. Early Onset Schizophrenia (EOS) manifests in childhood or adolescence and represents a more severe variant of the Adult Onset form of the disorder (AOS). EOS offers a unique opportunity of exploring the impact of disease related mechanisms on the developmental trajectory of cognitive function. The present review focused on the domains of general intellectual ability (IQ), attention, executive function and memory. Significant methodological variability was noted across the different studies that examined these aspects of cognition in EOS patients. Despite this, a consistent pattern emergent from the data suggesting that (a) EOS patients compared to healthy children and adolescents show impairments of medium to large effect size in IQ, attention, memory and executive function (b) despite increased clinical severity, the cognitive profile of EOS patients is comparable to that of AOS patients (c) healthy adolescents show age-related improvement in their ability to perform tests of attention, memory and executive function; this is not present in EOS patients thus resulting in increased age-related deviance in patients' performance. This apparent decline is mostly attributable to patients' failure to acquire new information and to use more sophisticated cognitive strategies.

Keywords: cognition, childhood, adolescent, schizophrenia, intelligence, memory, executive function, attention

INTRODUCTION

Early Onset Schizophrenia (EOS), regardless of whether it presents in childhood (childhood onset schizophrenia; COS) or adolescence (adolescent onset schizophrenia; AdOS) lies on the same diagnostic continuum with the adult onset (AOS) form of the disorder (Asarnow et al., 1994; Nicolson and Rapoport, 1999); longitudinal studies have confirmed the phenotypical continuity of EOS with adult onset cases since schizophrenia diagnosed in childhood and adolescent shows high diagnostic stability even over 40 years of follow-up (Remschmidt et al., 2007). Similarly brain imaging studies have also established a neurobiological continuum between early and adult onset schizophrenia (Thompson et al., 2001; Greenstein et al., 2006; Burke et al., 2008; Kyriakopoulos et al., 2009).

However, EOS is associated with more severe clinical course (Werry et al., 1991; Eggers and Bunk, 1997), greater premorbid abnormalities (Watkins et al., 1988; Cannon et al., 2002; Vourdas et al., 2003), greater genetic loading (Asarnow, 1999) and developmental deviance (Hollis, 1995; Vourdas et al., 2003).

For more than two decades, the neurodevelopmental model has been the prevailing explanatory theory for the aetiology of schizophrenia. In its simplest form this model posits that schizophrenia is the behavioural outcome of aberrant neurodevelopment that begins long before the onset of clinical symptoms and is caused by a combination of environmental and genetic factors (Rapoport et al., 2005). In this context the study of EOS offers an opportunity to explore how disease related mechanisms may impact on facets of cognitive function and their developmental trajectories. This article presents a selective review of the relevant literature focusing on four key aspects of cognition, namely general intellectual ability, attention, executive function and memory.

GENERAL INTELLECTUAL ABILITY

In clinical EOS samples general intellectual ability has been most commonly assessed using the Intelligence Quotient (IQ) obtained from the full or short versions of the Wechsler Intelligence Scale for Children-Revised (WISC-R) (Wechsler, 1974) (ages 6–16 years) or Wechsler Adult Intelligence Scale – Revised (WAIS-R) (Wechsler, 1981) (17 years and older). In contrast epidemiological studies have used a variety of measures, their findings however appear consistent across studies and independent of the choice of test (Woodberry et al., 2008).

CROSS-SECTIONAL STUDIES

General Intellectual ability is compromised in EOS. Mean IQ in EOS patients has been consistently found to be about 1-1.5 standard deviations below the normative mean (Bedwell et al., 1999; Kumra et al., 2000; Kravariti et al., 2003b; Gochman et al., 2005; Fagerlund et al., 2006; White et al., 2006).

LONGITUDINAL STUDIES

Premorbid and prodromal phase

Epidemiological studies of healthy children and adolescents have established that (a) deviance from cognitive norm for general intellectual ability significantly increases the risk of schizophrenia and, that (b) schizophrenia patients as a group have lower premorbid IQ scores (Cannon et al., 2002; Reichenberg et al., 2005). This has been

confirmed further by a meta-analysis by Woodberry et al. (2008); the effect size of premorbid IQ decrement was medium but independent of any methodological considerations relating to sample characteristics such as age at the time of testing. They also reported IQ decline associated with the onset of psychotic symptoms. Bedwell et al. (1999) were amongst the first to report this observation in COS patients from the National Institute of Mental Health (NIMH) cohort. They noted a decline in the age-corrected (but not raw) IQ scores which began about 2 years prior to the onset of frank psychosis and continued for up to 2 years post-onset. The authors suggested that this apparent decline was related not to loss of function but to the inability of EOS patients to acquire new skills and information in line with their healthy adolescent counterparts.

Longitudinal, post-psychosis onset studies

Most of the evidence available suggests that general intellectual ability in EOS remains largely stable after the onset of psychosis. Gochman et al. (2005) analysed IQ data from 70 COS patients from the NIMH cohort. With the exception of 13 patients for whom earlier IQ scores were available, baseline IQ measures were obtained after the onset of psychosis during the patients' initial assessment at the NIMH. Patients were followed up for 8 years with further IQ evaluations at 2-year intervals. Over this lengthy follow-up period, IQ scores fluctuated but there was no significant overall change. In contrast to earlier observations by Bedwell et al. (1999), in this larger NIMH sample raw scores for the information, comprehension and picture arrangement subscales increased significantly over time. Frangou et al. (2008) reached very similar conclusions when examining longitudinal IQ data from 20 EOS patients and their matched healthy controls from the Maudsley Early Onset Schizophrenia Study. In this cohort, IQ was assessed on two occasions, once within the first two years from the onset of psychosis and then on average 4 years later. Both patients and controls showed a small but statistically significant improvement in their IQ score between baseline and follow-up assessments.

COMPARISON TO ADULT ONSET SCHIZOPHRENIA

Despite increased illness EOS patients appear to have comparable deficits to AOS patients with respect of general intellectual ability. A study of Indian EOS patients is the only one to have found greater IQ impairment in COS than adult onset schizophrenia with AdOS patients occupying an intermediate position (Biswas et al., 2006). In all other studies no significant differences in IQ were reported between COS, AdOS (Rhinewine et al., 2005) and AOS samples (White et al., 2006). White et al. (2006) have undertaken the only study to date to directly contrast the cognitive profiles of EOS of AOS patients. Their study sample comprised of 49 adolescents with COS or AdOS, 139 AOS patients with first episode schizophrenia and 272 healthy volunteers (32 adolescents and 240 adults). General intellectual function was evaluated with the WAIS-R which yielded nearly identical IQ scores for both patient groups; these were approximately 1 standard deviation below the mean IQ of the healthy controls.

ATTENTION

The nature and degree of attentional impairment in EOS remain unclear due to significant between-study variability. This probably relates both to the sensitivity of the neuropsychological tests used and the size and clinical features of study samples. Although attention underpins cognitive function in general there are several tests that are conventionally construed as relatively specific assays of different aspects of attention. In the literature reviewed here attention was commonly assessed using the Trails Making Test (TMT; Reitan, 1995) and particular subtests of the WISC-R and WAIS-R. Versions of the Continuous Performance Test (CPT) and the dichotic listening test were used to evaluate sustained and selective attention respectively.

CROSS-SECTIONAL STUDIES

Kumra et al. (2000) reported that COS patients from the NIMH cohort showed marked attentional dysfunction. Their observation was based on data from the TMT and the Coding, Digit Symbol and Digit Span subtests of the WAIS-R or WISC-R which were used to form a composite measure of attention. Patients scored about two standard deviations below the normative mean. Øie and Rund (1999) reported that their sample of 19 EOS patients were not significantly impaired in sustained attention, as measured by the Degraded Symbol CPT (DS-CPT; Nuechterlein and Dawson, 1984), or in selective attention as assessed using a dichotic listening task. The TMT and the Digit Symbol subtest of the WISC-R were used to form a summary measure of "visuomotor processing and attention". Patients scored about two standard deviations below the control mean on this particular variable. Brickman et al. (2004) grouped the Digit Span subtest of the Wechsler intelligence scales and the TMT to form a composite variable for attention. Their sample comprised of 39 never medicated adolescents with first episode psychosis whose score was nearly 3 standard deviations below that of controls on this particular variable. Additionally, an impairment of nearly two standardar deviations compared to controls was noted in a version of the Digit Span in a sample of 34 young people with schizophrenia and related disorders (Karatekin et al., 2008). In contrast, data from the Maudsley Early Onset Schizophrenia Study did not reveal attentional deficits in EOS patients compared to matched controls (Kravariti et al., 2003a). Attention in this study was measured using the Attention/Concentration factor of the WMS-R and selective attention was evaluated using a dual task paradigm.

LONGITUDINAL, POST-PSYCHOSIS ONSET STUDIES

The issue of age-related changes in attention in EOS patients has been explored in three different samples. Thaden et al. (2006) administered the Continuous Performance Test-Identical Pairs (IP-CPT; Cornblatt et al., 1988) to 59 EOS adolescents and 55 matched normal controls. Across the age span of the sample (10–20 years of age) healthy adolescents improved in task performance and this was particularly true for task conditions with high processing load. This was not present in patients, suggesting a failure in the developmental trajectory that underpins increased attentional capacity with age. Frangou et al. (2008) and Øie and colleagues (Øie and Hugdahl, 2008; Øie et al., 2008) examined longitudinal data from the Maudsley Early Onset Schizophrenia Study and from a Norwegian sample of EOS patients followed-up over an average period of 4 and 13 years respectively. Both studies reported that EOS patients showed a decline in attentional measures. Their age-matched healthy counterparts showed age-related improvements in attentional processing which was absent in EOS patients.

COMPARISON TO ADULT ONSET SCHIZOPHRENIA

When contrasting EOS and AOS patients to healthy controls, White et al. (2006) combined four tasks to compose the summary variable corresponding to the domain of attention; these were the CPT (Conners and Staff, 1995), the Circle A Letter-cancellation task (Talland and Schwab, 1964), the Stroop Color and Word Test (Golden, 1978), and the TMT. Both EOS and AOS patients performed worse than healthy controls in this domain but there was no difference between the two patient groups.

EXECUTIVE FUNCTION

Executive function emerged as a concept in neuroscience mostly based on the association between frontal lobe integrity and behaviours such as problem solving, response inhibition, strategy development and implementation and working memory. Elliott (2003) proposed that executive functioning can be defined as the complex process of coordinating multiple sub-processes to achieve a particular goal. Given that multiple facets of cognition are currently considered constituent aspects of executive function it is not surprising that many different tests have been used to examine executive function in EOS. There are two issues that become apparent when reviewing the literature which are not specific to EOS but are pervasive in the field of cognitive research. Firstly, individual studies only test a limited range of cognitive processes that comprise executive function. However the presentation and interpretation of the results often refers to executive function as a whole thus potentially obscuring informative differences regarding aspects of executive function that may be affected or preserved. Secondly, there is no consensus with respect to tests of executive control of attention or memory which are attributed to specific cognitive domains depending on the authors' preferences.

CROSS-SECTIONAL STUDIES

Kenny et al. (1997) compared 17 EOS patients to an equal number of matched healthy adolescents using a broad neurocognitive battery. Test relevant to executive function included the tests of abstraction and perseveration, namely the Wisconsin Card Sorting Test (WCST; Heaton et al., 1993 and the maze subtest of the WISC-R, the Trigram Recall with Interference Test (Baddeley, 1986) and the coding subtest of the WISC-R (both considered tests of working memory) as well the Controlled Oral Word Retrieval (Benton, 1968) and Category Instance Retrieval Tests (Perret, 1974) that measure verbal fluency. The biggest effect size was noted for working memory (effect size 1.65–1.79), followed by abstraction and perseveration (effect size 0.61–0.68) and category retrieval (effect size 0.66). Øie and Rund (1999) in their sample of adolescent schizophrenics also found deficits in the WCST. Similar deficits in abstraction and cognitive set were also reported by the NIMH group (Kumra et al., 2000). In the Maudsley Early Onset schizophrenia study executive function was assessed using the Tower of London Test (TOL; Shallice, 1982) to measure planning and problem-solving and the Executive Golf task to measure spatial working memory (Kravariti et al., 2003a). In the TOL patients showed deficits in planning accuracy and reduced subsequent planning time (a measure of time spent planning and thinking about the next problem solving move), which may suggest greater impulsivity. This pattern was also observed by Fagerlund et al. (2006). Deficits in spatial working memory related mostly to EOS patients' inability to generate an efficient strategy and less so in maintaining information in working memory.

LONGITUDINAL STUDIES

Cervellione et al. (2007) found adolescent schizophrenic patients to have significant impairment in executive function which remained unchanged over a 2-year follow-up period. Similarly, Frangou et al. (2008) evaluated the stability of executive function in the Maudsley Early Onset Schizophrenia study with respect to planning as problem solving as reflected by the TOL. Although planning accuracy was lower in EOS patients, both groups' maintained the same level of performance over the 4-year follow-up period. Øie et al. (2008) focused on abstraction and perseveration using the WCST. The performance of EOS patients did not change over the 13-year follow-up period but they failed to show the improvements in perseverative errors that were noted in their healthy counterparts.

COMPARISON TO ADULT ONSET SCHIZOPHRENIA

White et al. (2006) examined two aspects of executive function, namely working memory and problem solving when comparing EOS to AOS patients and to controls. The composite measure of working memory comprised the arithmetic and digit span subtests from the WAIS-R and it was the only domain where EOS patients underperformed compared to AOS patients. The functional domain of problem solving included test performance on the Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993), the abstractions subtest from the Shipley Institute of Living Scale (Shipley, 1946) and the comprehension, similarities, picture completion and picture arrangement subtests from the WAIS-R. No differences between the patients groups were noted for the above variables.

MEMORY

Memory impairment is consistently reported in schizophrenia regardless of age of onset. Most studies assessing memory and learning in EOS have used versions of the Wechsler Memory Scales while the California Verbal Learning test (CVLT) (Delis et al., 1994) or similar list learning tasks have been widely used to measure verbal learning. Visual memory and learning are less commonly assessed, with the Kimura Recurring Figures Test (Kimura, 1980) being the most popular instrument employed.

CROSS-SECTIONAL STUDIES

Kenny et al. (1997) were amongst the first to report significant impairment in verbal memory and leaning in AOS patients compared to healthy adolescents. In their study verbal memory and learning were assessed using list learning tests (Buschke and Fuld, 1974) while immediate and delayed recall were assessed using the Logical Memory I and II subtests of the WMS-R (Wechsler, 1987). EOS patients underperformed in all measures of verbal learning and memory and in delayed (effect size range 0.68–0.96) but not immediate recall. The study by Øie and Rund (1999) suggested that visual memory (assessed using the Kimura Recurring Figures Test) is also significantly impaired in EOS; the performance of their sample of AOS patients was on average two standard deviations below that of healthy adolescents. Ueland et al. (2004) also observed significant visual memory impairment in adolescents with schizophrenia

spectrum disorder also using the Kimura Recurring Figures Test. However, visual memory (as assessed with the Wechsler Memory Scale-Revised; WMS-R) was only minimally affected in EOS patients from the Maudsley Early Onset Schizophrenia Study (Kravariti et al., 2003b) while significant impairment was again noted for verbal memory. Brickman et al. (2004) confirmed this finding in a sample of 29 never-medicated first-episode adolescents with psychosis where verbal memory and learning was assessed with a list learning task and was found to be significantly impaired in patients compared to controls. A similar finding was also reported by Landrø and Ueland (2008) who also examined verbal memory and learning using a list learning test when comparing 21 adolescents with schizophrenia spectrum disorders to healthy adolescents. Furthermore, the authors observed that the impairment primarily affected learning rather than recognition or recall. Roofeh et al. (2006) used the CVLT to further delineate the nature of the verbal memory and learning deficits in adolescents with schizophrenia and schizophrenia spectrum disorders. They found large impairments in patients compared to healthy controls in verbal learning, immediate and delayed recall, recognition memory and consistency of recall, but not in measures of rate of forgetting, proactive or retroactive interference or serial order effects in recall such as primacy and recency. Furthermore, in healthy individuals there was an age related switch in encoding and retrieval from serial recall to semantic clustering. Young patients with EOS and spectrum disorders failed to make this developmental change in memory organisation and retrieval.

LONGITUDINAL, POST-PSYCHOSIS ONSET STUDIES

Cervellione et al. (2007) found verbal learning and memory (as assessed with the CVLT) to be impaired in adolescents with schizophrenia but stable over a 2-year follow-up period. However, in the 4-year follow-up of the EOS sample from the Maudsley Early Onset Schizophrenia Study (Frangou et al., 2008), patients showed evidence of decline in the verbal memory index of the WMS-R while healthy adolescents performed at the same level on both assessments. Careful examination revealed that this decline affected primarily acquisition of new information rather than consolidation and recall. Øie et al. (2008) reached the same conclusions using the CVLT; over a 13-year follow-up period healthy controls showed no change in their performance while EOS patients' performance in the total learning trials declined.

COMPARISON TO ADULT ONSET SCHIZOPHRENIA

According to Basso et al. (1997) verbal memory performance differentiated AdOS from AOS patients and controls being significantly more impaired in AdOS particularly in measures of immediate recall. White et al. (2006) compared EOS and AOS patients to matched controls on two composite measures of verbal and non-verbal memory. The former included variables from a list learning test, the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1958) and the logical memory subtest of the WMS-R. The latter included the immediate and delayed recall trials of the Rey-Osterrieth Complex Figure Test (ROCFT; Rey, 1941; Osterrieth, 1944) and the total number correct from the Benton Visual Retention Test-Revised (BVRT-R; Benton, 1974). The two patient groups did not differ in either verbal or non-verbal memory.

CONCLUDING REMARKS

This review examined the cognitive profile of EOS patients in terms of general intellectual ability, attention, executive function and memory. Despite significant differences in sample characteristics and cognitive tests employed a remarkably consistent pattern emerges from the overall literature. The evidence reviewed suggests that (a) EOS patients are impaired in all four domains examined (b) the degree of impairment in all four domains is comparable to that seen in AOS patients with the possible exception of working memory where EOS patients may be more impaired (c) there is little evidence for decline in any of the four domains, at least for up to 13 years post illness onset and (d) increased deviance in EOS patients as they moved into adulthood was noted for attention, memory and executive function but this was mostly due to patients' failure to show the age-related improvements in these domains compared to their healthy counterparts.

Speculation as to the potential mechanisms underlying the cognitive patterns identified is beyond the resolution of the data reviewed here. Additionally inferences about neural systems based solely on behavioural performance on cognitive tests can only be made with caution. However, it could be argued that, in EOS, the combination of relative stability in cognitive "dysfunction" coupled with lack of age-related improvement in cognitive abilities resonates with brain imaging findings relating to the brain's maturational trajectory. Longitudinal studies of normally developing individuals have shown that primary motor and sensory areas mature early while areas subserving more complex functions follow a back-to-front pattern starting at the parietal lobes and progressing towards frontal and temporal regions (Gogtay et al., 2004; Sowell et al., 2004). Recent longitudinal studies suggest in EOS patients grey matter maturation shows an abnormal trajectory with lower and later peaks than for healthy subjects (Douaud et al., 2009). This altered brain developmental time course is in line with the abnormal developmental course suggested by cognitive data.

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Cognitive impairments in schizophrenia as assessed through activation and connectivity measures of magnetoencephalography (MEG) data

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The cognitive dysfunction present in patients with schizophrenia is thought to be driven in part by disorganized connections between higher-order cortical fields. Although studies utilizing electroencephalography (EEG), PET and fMRI have contributed significantly to our understanding of these mechanisms, magnetoencephalography (MEG) possesses great potential to answer long-standing questions linking brain interactions to cognitive operations in the disorder. Many experimental paradigms employed in EEG and fMRI are readily extendible to MEG and have expanded our understanding of the neurophysiological architecture present in schizophrenia. Source reconstruction techniques, such as adaptive spatial filtering, take advantage of the spatial localization abilities of MEG, allowing us to evaluate which specific structures contribute to atypical cognition in schizophrenia. Finally, both bivariate and multivariate functional connectivity metrics of MEG data are useful for understanding how these interactions in the brain are impaired in schizophrenia, and how cognitive and clinical outcomes are affected as a result. We also present here data from our own laboratory that illustrates how some of these novel functional connectivity measures, specifically imaginary coherence (IC), are quite powerful in relating disconnectivity in the brain to characteristic behavioral findings in the disorder.

Keywords: magnetoencephalography, functional connectivity, resting-state, schizophrenia, executive function

INTRODUCTION

The clinical and cognitive features of schizophrenia are believed to be due, at least in part, to impairments in the activity of – and the interactions in activity between – functionally critical brain regions (Friston and Frith, 1995; Gold and Weinberger, 1995). The hypothesis that schizophrenia is a "disconnection syndrome" dates back to Bleuler, with the implication that disordered thought processing, social function and cognitive abilities are the result of a "splitting" of mental faculties. The general interpretation of this disconnection hypothesis has been that, in schizophrenia, reduced activity or undercoupling within key brain networks leads to an inability to efficiently modulate incoming neural processes. Only recently, with the advent of non-invasive imaging techniques, has direct evidence for this failure of brain function in schizophrenia been available. Changes in activity and connectivity identified through these methods support a consensus that schizophrenia is the net result of an inability to effectively integrate and process information in the central nervous system, contributing to aberrant patterns of cognition and behavior. However, our understanding of how this failure of integration relates to behavioral performance and illness symptoms in schizophrenia is far from complete. The goal of this article is to overview the role of magnetoencephalography (MEG), an imaging technique with exquisite spatial and temporal resolution, in linking brain function to cognition and disease states in schizophrenia.

EVIDENCE FOR FUNCTIONAL DISCONNECTIVITY IN DTI, fMRI, PET AND ELECTROENCEPHALOGRAPHY

The disconnection hypothesis has been recently supported by imaging studies which have shown altered patterns of anatomical brain connectivity in patients with schizophrenia using techniques such as diffusion tensor imaging (DTI; see Kubicki et al., 2005; Kyriakopoulos et al., 2008 for a review). DTI, which measures the diffusion of water molecules along white-matter fiber tracts in the brain, has been a successful approach in demonstrating abnormalities in neural circuitry within this population. These differences in connectivity are often between brain regions associated with higher-order cognitive processing and executive function (Dwork et al., 2007). One consistent finding is that the fractional anisotropy (a DTI index representing the fraction of the tensor that contributes to the anisotropic diffusion) is reduced in patients with schizophrenia (Ardekani et al., 2003; Burns et al., 2003; Kumra et al., 2004). While these studies are highly informative, it is unclear how these deficits in neuroanatomical connectivity directly relate to cognitive impairments identified in patients with schizophrenia.

Consistent with data from DTI, investigations of functional connectivity in PET and functional MRI data both during cognitive tasks (see Ragland et al., 2007; Potkin and Ford, 2009 for a review) and at rest (see Grecius, 2008 for a review) support the hypothesis of neural disconnectivity in schizophrenia. Although related to anatomical connectivity, studies of functional connectivity

instead focus on how processing between multiple brain regions are correlated and how information is parsed between multiple nodes of a network (Friston, 1994; Ramnani et al., 2004). Although the notion of "disconnection" in schizophrenia tacitly assumes that an overall pattern of underconnectivity will be identified in this patient population, both increases and decreases in functional connectivity have been identified in this group.

While these investigations of functional connectivity in fMRI and PET are extremely informative, especially at a spatial level, there are significant areas of research that simply cannot be accessed by these imaging methodologies. The sampling resolution of either technique generally occurs, at best, on the order of seconds, which makes it extremely difficult to evaluate how information flows between brain regions. In executive function, information is not only transferred between cortical regions at a rapid rate (on the order of milliseconds) but is also thought to be dependent on processing in different oscillatory domains (alpha, beta, gamma, etc.). Therefore, fMRI and PET are ideal at reconstructing brain activity at very low frequencies (<0.1 Hz) and, presently, are unable to parse out activity in higher frequency bands known to exist in mammalian cortex.

In the human brain, oscillatory activity at high frequencies has traditionally been studied non-invasively using electroencephalography (EEG). Functional connectivity can be examined in EEG by looking at coupling between specific sensors through techniques such as coherence, and a number of studies have demonstrated deviations in sensor coherence in patients with schizophrenia (Leocani and Comi, 1999). There is a lack of agreement in the literature with respect to changes in EEG coherence in schizophrenia, with some studies illustrating increased functional connections in patients (Ford et al., 1986; Merrin et al., 1989) while others have reported reduced sensor coherence (Merrin and Floyd, 1992; Tauscher et al., 1998) or no differences at all (Wada et al., 1998). While it has been proposed from these EEG studies that compromised interactions between the frontal and temporal lobe are a primary feature of schizophrenia (Ford et al., 2002; Strelets et al., 2002; Winterer et al., 2003) the spatial limitations of EEG prevent us from knowing exactly which regions are affected in the disorder.

Magnetoencephalography has begun to receive attention in imaging research as having direct applications to the study of impaired cognitive processes in clinical populations, including schizophrenia (Reite et al., 1999; Näätänen and Kähkönen, 2009). There are significant advantages to using MEG to study neural processes, especially when modeling how activity within a cortical field can influence and interact with activity in other parts of the brain. First, like EEG, MEG is able to reconstruct neural activity on the order of milliseconds. Secondly, recording from MEG sensors allows investigators to access oscillatory neural activity in higher frequency ranges (e.g. alpha, beta, gamma) than those attainable in both fMRI/PET. In addition, the sampling frequency of data acquisition in MEG (generally greater than 1 kHz) is not limited by electrode impedance (as in EEG), permitting the examination of ultra-high frequency (>100 Hz) brain activity in this modality. Thirdly, volume conduction artifacts commonly found in other imaging modalities are significantly reduced in MEG, as structures such as the skull and CSF do not interfere with the propagation of the magnetic fields (Leahy et al., 1998). Finally, novel source localization algorithms allow high-fidelity reconstruction of whole brain activity, also referred to as electromagnetic brain imaging (EBI). EBI provides information about where changes in observed neural activity in MEG data arise in the brain (Robinson and Vrba, 1999; Sekihara et al., 2001; Dalal et al., 2008). The application of EBI is particularly useful for examining changes in timing between disconnected regions identified in DTI and fMRI studies, because of its superior time-scale.

In this article, we will review how MEG, and especially EBI, has been applied to examining impaired social, emotional and cognitive processing in patients with schizophrenia. Special attention will be paid to how studies use MEG to investigate functional connectivity. Finally, we will review some novel metrics for estimating neural interactions in MEG and how these techniques can be applied to further our understanding of the neural mechanisms affected in schizophrenia.

COGNITIVE IMPAIRMENTS IN SCHIZOPHRENIA AS ASSESSED BY MEG SENSOR DATA

Many of the studies that examine MEG sensor data in schizophrenia have been extensions of EEG studies, where a change in the averaged amplitude at a particular sensor, during a cognitive paradigm, is interpreted to represent aberrations of cortical processing. With the improved spatial resolution of MEG, these studies both independently confirm findings from EEG studies, as well as expand our knowledge of the specific brain regions that contribute to cognitive dysfunction in the disorder.

INFORMATION FILTERING AND SENSORY GATING

A reduction in the positive deflection of the EEG waveform around 50 ms following the onset of a repeated stimulus (P50) is thought to represent the attenuation of irrelevant information. This level of filtering of an incoming sensory stimulus, referred to as "sensory gating", is known to be compromised in patients with schizophrenia (Adler et al., 1982). An inability to separate relevant from irrelevant sensory stimuli is putatively related to sensory overload and distractibility, thereby impacting higher-order cognitive function (attention, maintenance of working memory, self-regulation). Examination of the magnetic component of the P50 (M50) has provided detail about the spatial and temporal characteristics of this mechanism in auditory processing. Standard examinations of sensory gating are generally computed from EEG sensor recordings at a midline location (electrode Cz) providing no information about the origin of the source or hemispheric lateralization effects.

Initial MEG studies have been able to localize the source of the M50 in an auditory stimulus train to the bilateral superior temporal gyrus (STG; Reite et al., 1988). In schizophrenia, impaired sensory gating of the M50 is lateralized, with insufficient sensory gating of an auditory stimulus within the M50 response located in the left hemisphere (Thoma et al., 2003). This lateralized effect in left auditory cortex was also found to be significantly and positively correlated with poor working memory in patients with schizophrenia (Thoma et al., 2003). It has been suggested that such a failure of sensory gating in schizophrenia is due to faulty functional connectivity between the STG with deep brain structures involved in sensory filtering (see Huang et al., 2003). Concurrent EEG/MEG recordings during a paired-click paradigm have shown that while

MEG sources in bilateral STG reliably account for most of the P50 EEG component at Cz in healthy control subjects, residual high-gamma activity (~40 Hz) persists in patients with schizophrenia once the STG sources are accounted for (Huang et al., 2003).

In the frequency domain, a reduced M50 in schizophrenia is thought to be due to faulty habituation of oscillations in the gamma range, possibly due to noisy cortical sources contributing to this signal (Clementz et al., 1997). When sensory gating in the auditory system becomes deficient, it potentially influences downstream processes that are dependent upon efficient filtering represented in the M50, including the component that occurs 100 ms following the stimulus (the M100). In schizophrenia, both the M50 and the M100 have been independently shown to be impaired (Clementz et al., 1997; Thoma et al., 2003). This lack of sensory gating can make it difficult for the patient to discriminate between environmentally relevant sources of auditory information and may have profound effects on higher-order cognition. For example, recent work by Dale et al. (2009) has demonstrated that when successive speech syllables are presented within auditory noise, the M100 response to the second stimulus is significantly and abnormally "unattenuated" in patients with schizophrenia. This lack of M100 attenuation was correlated with poor task accuracy and low global cognition scores (Dale et al., 2009).

Functional interactions between the M50 and the M100 in schizophrenia have also been examined using MEG. In a study by Hanlon et al. (2005), auditory sensory gating was examined using a dual-click experiment during MEG recordings, and hierarchical linear regression was used to model coupling between sensory gating in the M50 and M100 sources. In the patient group, a left lateralized reduction in M50 sensory gating and bilateral reduction in M100 sensory gating suggested that unrestricted, robust signal at 100 ms was the net result of failure in gating information from an early response (**Figure 1**). Impaired sensory gating represented in the M100 response was associated with a gating deficit in the M50 from source localizations over left auditory cortex, indicating that a failure to properly filter incoming signals through the M50 affected downstream processing in the M100. This relationship between M50 and M100 sensory gating for right hemisphere sources was not significant (Hanlon et al., 2005). Developed connections between non-essential cortical fields can interfere with sensory gating and auditory processing. In concurrent EEG/MEG recordings, while no significant relationship has been identified between a EEG P50 component and symptom ratings, a failure of sensory gating of the right M50 component (but not the left) has been shown to be positively correlated with negative symptom scores (Thoma et al., 2005). This is in contrast to a relationship between impaired sensory gating in the left hemisphere, which is correlated with attention and working memory (Thoma et al., 2003). Although these lateralization effects are still under investigation, they are consistent with models of compromised fronto-temporal function in schizophrenia.

The extent to which this impairment in sensory gating generalizes across sensory modalities in schizophrenia is presently unclear. Responses to tactile stimuli in primary somatosensory cortex (S1) and secondary somatosensory cortex (S2) have also been examined in these patients using MEG. These studies have demonstrated that gating ratios for an early somatosensory evoked response (M20) in S1 are relatively intact in schizophrenia (Edgar et al., 2005; Thoma et al., 2007), while sensory gating of the late response (M80) in S2 is profoundly affected in these patients (Thoma et al., 2007), Although this argues against a broad deficit in cross-model processing in schizophrenia, it is consistent with a general notion of filtering impairments across sensory systems in this condition.

DETECTION OF SALIENT EVENTS IN SCHIZOPHRENIA: MISMATCH NEGATIVITY (MMN)

One cortical process extensively studied through MEG is the automatic response that is generated following a deviant stimulus in a train of auditory standards, or the mismatch negativity effect (MMN, or the magnetic equivalent, MMNm). This evoked response, which occurs 150–200 ms following a deviant stimulus, is thought to reflect, in healthy individuals, a pre-attentive process whose purpose is to reorient the individual towards a novel stimulus that has entered the environment (for a review, see Pulvermüller and Shtyrov, 2006). In patients with schizophrenia, the amplitude of the MMNm is generally reduced, across experimental designs and stimulus types (**Figure 2**, see Kasai et al., 2002; Kircher et al., 2004;

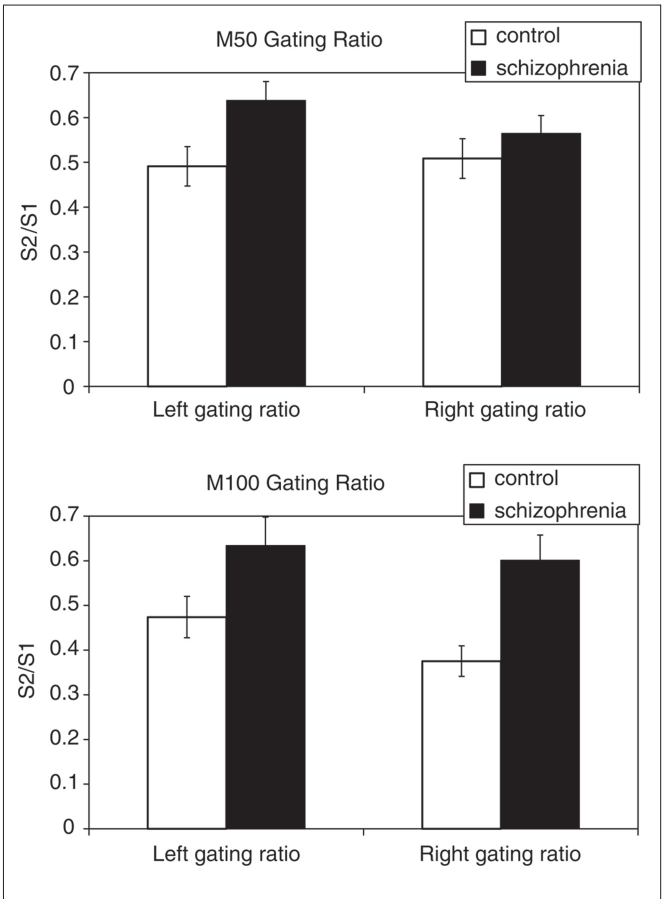

FIGURE 1 | Auditory sensory gating responses (indexed as a ratio in sensor power between the response to the second (S2) and first (S1) auditory click) in both patients with schizophrenia and controls. Auditory gating ratios at both 50 ms (M50) and 100 ms (M100) following stimulus presentation are significantly greater in the patient group in the left hemisphere. In the right hemisphere, reduced sensory gating in the patient group was only significant for a M100 response. Error bars = SE mean. Reproduced, with permission, from Hanlon et al. (2005).

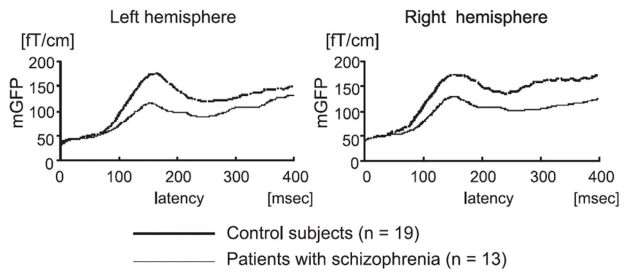

FIGURE 2 | Mismatch negativity (MMN) in healthy control participants and in patients with schizophrenia. Changes in grand magnetic field power (mGFP) over auditory cortex in response to a deviant stimulus (phoneme change) are significantly reduced in patients with schizophrenia bilaterally. Reproduced, with permission, from Yamasue et al. (2004).

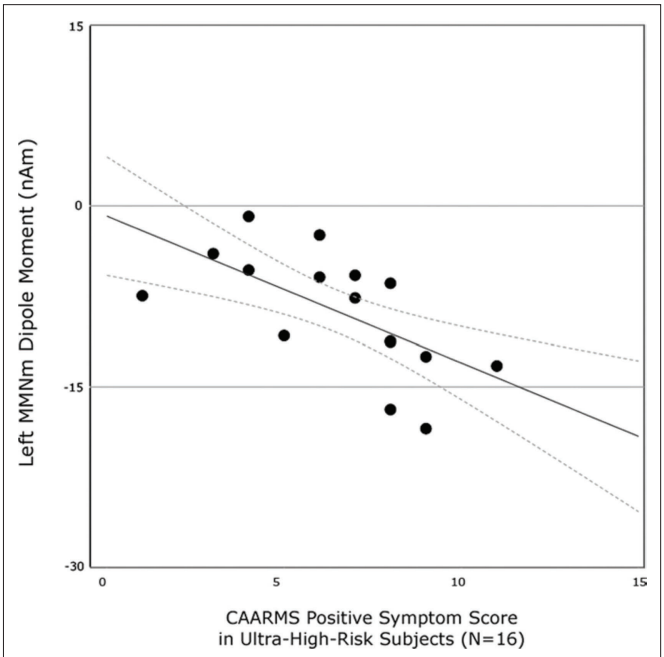

FIGURE 3 | Correlations between MMN measures in patients during the prodromal phase of the disorder with an assessment of ultra-high risk state (CAARMS). A negative relationship is seen between MMN strength and ranking on the CAARMS metric. Reproduced, with permission, from Shin et al. (2009).

Yamasue et al., 2004; Thönnessen et al., 2008). In schizophrenia, this deviation in MMNm is best produced in an optimum design paradigm (Näätänen et al., 2004), where the deviant occurs much more frequently in the stimulus train and is modified along one feature throughout stimulus presentation (either its frequency, intensity, duration, sound source or gap in tone, see Thönnessen et al., 2008). The MMNm is thought to be bilateral for categorical speech sound deviants (Kasai et al., 2002) and low MMNm amplitude may be due to, in part, reduced gray matter volume in the cortex along the planum temporale found in patients with schizophrenia (Yamasue et al., 2004). The demonstration of compromised gray matter density (and thus cortical function) in the temporal lobes of these patients are congruent with work in combined fMRI/MEG studies that examine MMNm in the patient and control group using both neuroimaging modalities (Kircher et al., 2004). In this study, reduced MMNm in patients with schizophrenia correlated with a decrease in BOLD signal in STG, along the planum temporale (secondary auditory cortex) but not in primary auditory cortex, along Heschl's gyrus (Kircher et al., 2004). Although a difference in MMN amplitude between patient and control groups is readily identifiable in averaged EEG sensor data, the sources that contribute to this deviation are likely to be far more complex than just reduced activity within secondary auditory areas. MMN represents a powerful and well-developed experimental paradigm used to assess auditory processing dysfunction in schizophrenia.

A reduced MMN component measured through MEG may eventually prove to be a useful biomarker in determining susceptibility to schizophrenia, as in the case of ultra-high risk (UHR) individuals in the prodromal stage of the disorder. A recent study by Shin et al. (2009) demonstrated that this impairment in MMNm is persistent even before the onset of symptoms in schizophrenia. When compared to control participants, smaller magnetic field changes over auditory cortex in the left hemisphere were found in ultra high-risk subjects. Furthermore, MMNm amplitude was negatively correlated with measures of at-risk mental states (CAARMS) in the UHR group (**Figure 3**).

EMOTIONAL PROCESSING

An inability to extract relevant emotional content from a facial expression in order to guide behavior is thought to be a fundamental component of the broad social cognitive dysfunction found in patients with schizophrenia (Krong and Moran, 2008; Kohler et al., 2009). MEG studies of facial emotion processing have been able to examine the stages of cortical processing that are impaired in these patients (Rockstroh et al., 2006). Healthy individuals were able to discriminate between stimuli that are either emotionally charged or neutral, even when the stimuli were presented at a very high rate of visual stimulation (~4 Hz; Junghöfer et al., 2003; Peyk et al., 2008). Although patients with schizophrenia are able to make similar judgments of emotional valence, data from MEG sensors during this task suggest that this information is incorporated in an atypical fashion. Following an emotionally arousing visual stimulus, changes in amplitude normally seen in the posterior MEG sensors are markedly reduced in patients (Rockstroh et al., 2006). The timing of this deficient response fell over the range of 90–300 ms following the visual stimulus. While this deviant response did not compromise the patients' accuracy in detecting emotion, it is possible that it contributes in some as yet unidentified manner to the impaired social abilities seen in schizophrenia.

SPONTANEOUS CORTICAL ACTIVITY

Similar to what has been done in fMRI, EEG and PET, MEG has been used to examine deviations in resting-state cortical activity in patients with schizophrenia. Early investigations of low-frequency oscillations have shown that, in this group, stronger delta and theta (2–6 Hz) power at rest occurred along with a reduction in alpha power in the same sample (Cañive et al., 1998; Sperling et al., 2002). This increase in slow-frequency (<6 Hz) oscillations measured in MEG is likely due to a non-specific increase in the dipole moment amplitude across sensors for delta power, while an increase in theta

power might originate from an increase in parietal, temporal and occipital sources (Fehr et al., 2001, 2003). Fluctuations in delta and theta power in MEG have also been shown to be related to positive and negative symptoms assessed in these patients (Fehr et al., 2001, 2003). Sperling et al. (2002) were also able to relate this increase in the 2–6 Hz range at rest with positive symptoms, with a positive correlation between power over temporal and parietal sources and PANSS ratings in patients with paranoid hallucinatory schizophrenia. A tight relationship between symptom measures and neural oscillations, which persist in the absence of behavior, demonstrates the pervasiveness of the neural dysfunction in schizophrenia. These changes in spontaneous cortical activity may or may not be driven by changes in connectivity between brain regions.

OTHER COGNITIVE FUNCTIONS

A number of other classical experimental designs in cognitive psychology have been adapted for use with MEG. For tasks such as mental arithmetic, MEG has been used to demonstrate both reductions in high-gamma sensor power (Kissler et al., 2000) and increases in delta and theta band activity (Fehr et al., 2003) in patients with schizophrenia. Disorganized brain activity (source clustering) recorded in MEG data during a categorical picture-naming task has also been shown to be present in patients with schizophrenia, and this impaired neural activity has been shown to be related to both positive and negative symptoms (Löw et al., 2006). In addition, examination of high-frequency cortical activity in MEG in response to speech stimuli has also been demonstrated to be related to clinical symptom scores. In patients with schizophrenia, the processing of speech sounds in the gamma (25–40 Hz) range over left auditory cortex is delayed, and negatively correlated with the severity of auditory hallucinations (Hirano et al., 2008; **Figure 4**).

LOCALIZING SEGMENTS OF NETWORKS AFFECTED IN SCHIZOPHRENIA: SOURCE-SPACE RECONSTRUCTIONS OF MEG DATA

Advances in EBI enable reconstruction of underlying brain activity from MEG sensor data. From the spatio-temporal patterns in the sensor data, it is now possible to reconstruct brain activity, also referred to as *sources*, using sophisticated and powerful algorithms that are also called "source reconstruction algorithms". An obvious advantage to examining data in source space is that the signals interpreted correspond to specific brain regions. However, the drawback to analyzing data in source space is that these algorithms attempt to solve an ill-posed inverse problem, wherein the number of unknown source locations is greater than the number of sensors. There have been significant advances in source localization algorithms in recent times that overcome several problems in EBI; and correspondingly, MEG studies have become synonymous with EBI.

There are currently a wide variety of *source localization algorithms* available for estimating source activity. Parametric dipole fitting is a common technique, where a small number of point dipole sources are assumed to generate the MEG data, and the problem reduces to determining parameters such as the location, orientation, and amplitude of these point dipolar sources. However this approach has issues with local minima and can be sensitive to the initialization of the number and location of dipoles (Mosher et al., 1992; Uutela et al., 1998). This initialization bias can be circumvented by automated dipole fit procedures, such as a multistart spatial–temporal downhill simplex algorithm (MSST) (Huang et al., 1998). Also, there are spatial scanning techniques that estimate the time course at every candidate location while suppressing the interference from activity at the other candidate source locations. Candidate locations for the source reconstructions are often constructed from an individual's MRI and can either occupy the entire volume, be constrained to the gray matter, or only lie on the cortical surface. Some examples of scanning techniques are minimum-variance adaptive beamforming and other variants of beamformers (Sekihara and Nagarajan, 2008), multiple signal classification (Mosher and Leahy, 1998), synthetic aperture morphometry (SAM) (Vrba and Robinson, 2001), dynamic imaging of coherent sources (DICS) (Gross et al., 2001), and source activity using knowledge of event timing for independence from noise and interference (SAKETINI; Zumer et al., 2007). An alternative approach to the scanning methods is to solve for the activity in all candidate source locations simultaneously, also referred to as a tomographic approach. There are a variety of tomographic

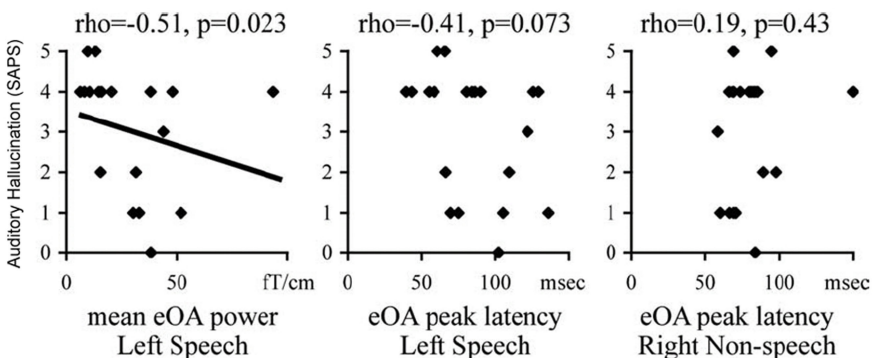

FIGURE 4 | Relationship between evoked oscillatory activity (eOA) in response to speech sounds in patients with schizophrenia to auditory hallucination scores as measured through SAPS. During the period of 100–150 ms following a speech sound, the magnitude of the eOA was negatively correlated with auditory hallucinations in the left hemisphere only. No significant relationship was seen between eOA latency and SAPS scores in either the left or right hemispheres. Reproduced, with permission, from Hirano et al. (2008).

methods such as minimum-norm estimate (Hämäläinen and Ilmoniemi, 1994), dynamic statistical parametric mapping (Dale et al., 2000), and standardized low resolution brain electromagnetic tomography (Pascual-Marqui, 2002). Some methods promote sparseness in the solution, where the majority of the candidate locations do not have significant activity; empirical evidence shows that a sparse source model can improve the accuracy of the localization in a noisy environment. Some sparse methods include focal underdetermined system solution (Gorodnitsky and Rao, 1997), minimum-current estimate (Uutela et al., 1999), and Champagne (Wipf and Nagarajan, 2009). One way to promote sparsity in the source activity is to use a L-1 norm instead of a L-2 norm in the minimized cost function (Uutela et al., 1999; Wipf et al., 2009), or alternatively use many recently proposed machine learning algorithms for reconstructing sparse sources (Wipf and Nagarajan, 2009; Wipf et al., 2009). While to date a small number of MEG studies in schizophrenia have used EBI techniques, as improvements in EBI continue to advance, it is expected that this number should significantly increase in the coming years.

COGNITIVE CONTROL

MEG sources have been modeled using adaptive spatial filters in order to reconstruct patterns of brain activity during a cognitive interference task (the Stroop task), in both healthy controls and patients with schizophrenia (Kawaguchi et al., 2005). This approach both localizes changes in the signal and provides information about the changes that occur over time. In healthy individuals, oscillatory activity in the gamma range (25–60 Hz) progressed from parieto-occipital to pre-frontal and primary motor cortex, over the time scale of 150–400 ms post-stimulus and pre-response (Ukai et al., 2002; Kawaguchi et al., 2005). In patients with schizophrenia that suffer from auditory hallucinations, additional activity was seen over right dorsolateral pre-frontal cortex (DLPFC) early on (~400 ms post-stimulus), a pattern not identified in the patient group without these symptoms (Kawaguchi et al., 2005). This data suggests that dysfunctional Stroop-like inhibition in patients with auditory hallucinations is not the result of aberrant information flow between brain areas in a cognitive control network. Instead, it appears that functionally irrelevant brain regions (such as right DLPFC) interfere with communication between relevant cortical fields.

WORKING MEMORY

During auditory working memory (e.g., Sternberg) tasks, a decrease in beta power within the sensors over auditory cortex occurs during the memory retention phase, a neural process known to be impaired (e.g., weak beta decrease) in patients with schizophrenia (Gruzelier et al., 1990; Reite and Rojas, 1997). However, a recent study by Ince et al. (2009) demonstrated that this impairment may extend beyond activity in the beta range. When patients were instructed to memorize a string of letters forming a word, separate patterns of activity in the delta, alpha, beta bands were readily identifiable from a classification of the MEG sensor data. Source-space projections derived from the classifications of the MEG data revealed that these changes in oscillatory power during the task specific to patients localized to superior frontal regions in the delta band, occipital cortex in the alpha range and frontal-temporal areas in the beta band (Ince et al., 2009). This type of categorization was not identified when subjects maintained a non-word in memory, consistent with the notion of language impairments in schizophrenia.

SPONTANEOUS CORTICAL ACTIVITY

Few studies have also reconstructed spontaneous cortical activity in source space from MEG sensor data. One particular focus has been on high-gamma activity during rest. In patients with schizophrenia, power at the MEG sensor level in the high gamma range (60–71 Hz) was found to be reduced at rest when compared to healthy controls (Kissler et al., 2000). A more recent study by Rutter et al. (2009) found that reconstructing data in source space using SAM provides some information about the origin of these changes in gamma power. The greatest reduction in power in the patients was in the 30–80 Hz range, and this reduction in gamma power was localized to medial parietal cortex (Rutter et al., 2009). Although this study did not use connectivity measures *per se*, the decrease in gamma power overlapped a region of the pre-cuneus known in functional MRI studies to be involved in introspective thought and also known to be functionally underconnected in patients with schizophrenia (Bluhm et al., 2007).

EXPLORING ABERRANT FUNCTIONAL CONNECTIVITY IN SCHIZOPHRENIA ACROSS MULTIPLE SOURCES THROUGH MEG

Ultimately, our understanding of neural activity and behavioral performance in schizophrenia is dependent not only on activity *within* an area during an active or inactive state, but also on how the brain integrates information *across* multiple sources. Although a common approach is to examine functional connectivity by using hemodynamic measures of brain activity (such as fMRI), MEG directly measures changes in the magnetic field induced by underlying neuronal currents, and is better suited for modeling these types of interactions. Decomposition of information across, space, time, and oscillatory domains yields complex information about how sources in the brain interact across many levels.

Ioannides et al. (2004) used MEG to examine functional connectivity in schizophrenia during emotional valence judgments in order to explore which segments of the cortical network are dysfunctional in the disorder. Patients were instructed to make decisions regarding the emotional content of the face (happy or sad) presented to the participant during MEG recordings. Interactions between brain sources were assessed using mutual information, a functional connectivity metric that evaluates the extent to which two cortical sources share a common time-series. Robust interactions between inferior frontal cortex, the fusiform gyrus (FG), primary and secondary visual cortex (V1/V2), and the amygdala were identified through functional connectivity analysis in healthy control subjects (**Figure 5A**). A markedly different pattern is seen in patients with schizophrenia, with reduced interactions between functionally critical brain regions during this task (**Figure 5B**).

Using MEG resting-state recordings, Georgopoulos et al. (2007) were able to discriminate not only between healthy controls and patients with schizophrenia, but also between patients and subjects with other clinical diagnoses. Data was acquired with the eyes open

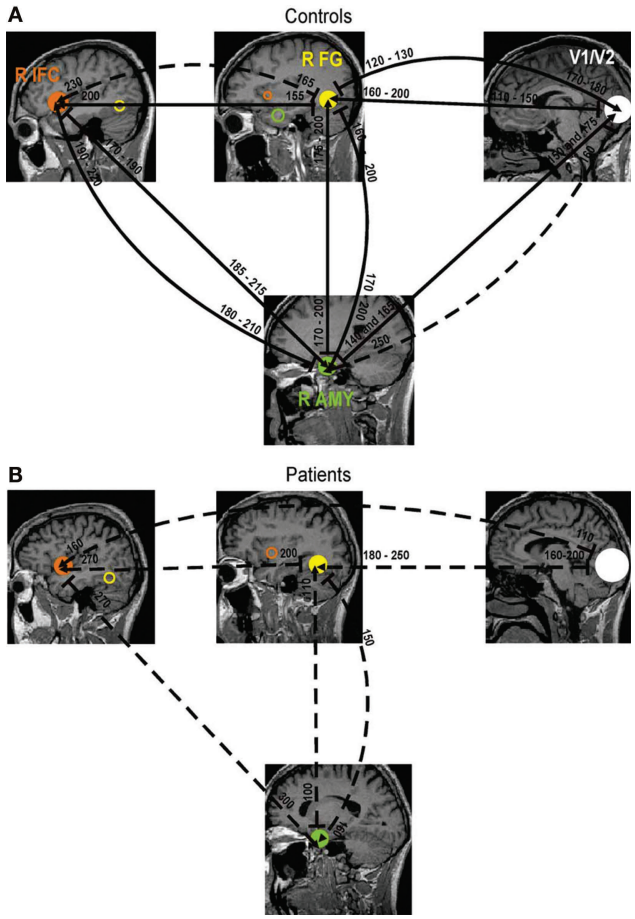

FIGURE 5 | Functional connections between brain regions active during an emotional processing task estimated through MEG. Robust influence amongst time courses (mutual information) can be derived between the right inferior frontal gyrus (IFG), FG, visual cortex (V1/V2) and amygdala (AMY) in healthy controls **(A)**. Coupling between these regions become more isolated in patients with schizophrenia, with reductions in the relatedness between two sources (dashed lines) as well as deviations in activation onset and latency **(B)**. Reproduced, with permission, from Ioannides et al. (2004).

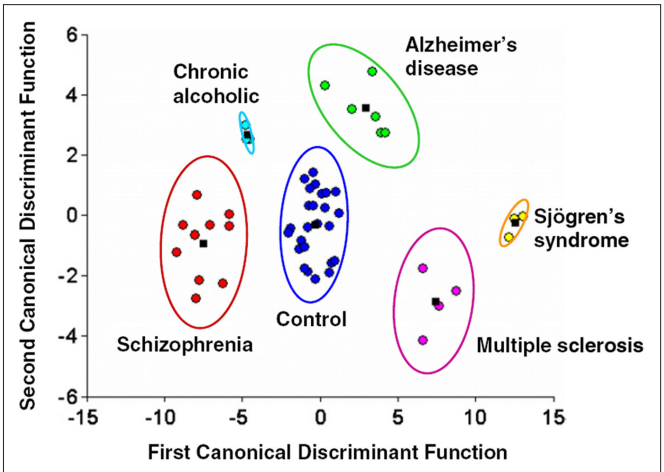

FIGURE 6 | Results from a linear discriminant classification analysis applied to MEG resting-state functional connectivity (partial cross-correlation) data across multiple groups, including both controls and patients with schizophrenia. Even from MEG recordings when no task is being performed, the classifier was able to discriminate between the different populations, with no overlap seen between the control and schizophrenia groups. These differences suggest that resting-state functional connectivity derived from MEG data can be a robust indicator of clinical diagnosis. Reproduced, with permission, from Georgopoulos et al. (2007).

for a short period of time (between 45 and 60 s) and functional connectivity was estimated by entering residuals (derived from an autoregressive moving average model) into a partial cross-correlation (PCC) analysis between all sensor pairs. In order to characterize a resting-state connectivity pattern distinct for patients with schizophrenia, PCC values were entered into a linear classifier, which separated connectivity patterns between subject groups. The network of connections measured by MEG at rest in the patient group was found to be non-overlapping with categorized activity of healthy controls (**Figure 6**). Similarly, these resting-state networks were distinct from patterns of connectivity in the other patient groups, including patients with Alzheimer's disease and Multiple sclerosis (Georgopoulos et al., 2007). Since no *a priori* network of connections were defined in this model, it illustrates that coherent, spontaneous activity recorded in MEG, even at the sensor level, can be used to separate clinical conditions like schizophrenia from unaffected populations.

NOVEL METRICS FOR ESTIMATING FUNCTIONAL CONNECTIVITY IN MEG

Despite the advantage of MEG (and EEG) in the temporal domain over fMRI, there have been relatively few publications that assess event-related or resting-state functional connectivity using MEG or EEG as compared to fMRI. There are two genres of metrics used in MEG functional connectivity: bivariate quantities are calculated in a pair-wise fashion between pairs of voxels and multivariate techniques model the interactions between several regions of interest. Likewise, functional connectivity metrics in MEG data analyses can be applied either in sensor-space or in source-space. Although many metrics have been proposed for functional connectivity in MEG, no careful comparisons have been made for the same dataset across bivariate and multivariate metrics. Here we provide a brief review of both bivariate and multivariate metrics applied to EEG and MEG data in source space and sensor space, as these techniques have the potential to reveal neural interactions compromised in schizophrenia.

BIVARIATE METRICS OF FUNCTIONAL CONNECTIVITY IN MEG

Bivariate metrics can be applied to MEG/EEG data in two ways. Since these metrics are computed between two time courses, they can either be computed between target sensors/voxels or they can be computed between all sensors/voxels and then an average connectivity value can be calculated for every sensor/voxel. The first of these methods is used when there is knowledge about the areas involved and can be considered a "hypothesis-driven" approach. The second, in contrast, can be described as a "data-driven" approach and is applicable when there is not *a priori* knowledge about which areas should exhibit high or changed connectivity. Correlation and its frequency domain analog, coherence, are the two most commonly used bivariate metrics in the literature (see Srinivasan et al.,

2007). An extension of using coherence on sensor time-courses, a source localization algorithm called DICS, is particularly designed to construct coherent activity by estimating time-courses and calculating magnitude coherence (Gross et al., 2001). There are also phase difference-based bivariate metrics that can be applied in similar fashion to the metrics described above. The difference in instantaneous phase between two time courses can be calculated using the Hilbert transform. There are different subsequent calculations that can be performed with the phase difference, e.g. phase coherence (PC), phase synchronization, index of synchronization (for examples, see Nikouline et al., 2001; Schoonhoven et al., 2003; Hadjipapas et al., 2005).

All types of bivariate metrics are susceptible to spurious interactions that arise from volume conduction artifacts in MEG and EEG recordings. The magnetic field or electric potential generated by a single neuronal source is picked up by not only the nearest sensor to the source, but the neighboring sensors also pick up the signal with a zero-time lag. This creates instantaneous blurring across the sensors. As such, the time-courses of many sensors can contain overlapping information due to this electromagnetic phenomenon, which can produce spurious interactions. Some bivariate metrics used for MEG and EEG functional connectivity analyses have been designed to overcome this blurring by isolating the non-zero-time-lag interactions from the zero-time-lag interactions, namely imaginary coherence (IC) and phase lag index (PLI). Both metrics are designed to assess only non-zero time lagged interactions in source or sensor data in order to cancel out the effects of cross-talk across the detection sensors.

Imaginary coherence is calculated by only considering the imaginary component of the complex-valued coherence. The imaginary part of the coherence is produced by non-instantaneous interactions between waveforms. It was found to be a better measure of coupling than the magnitude of coherence in an EEG experiment of voluntary finger movement (Nolte et al., 2004). PLI is similar to IC in that it includes only information that is transmitted at a non-zero time lag; any two signals that are instantaneously coupled and therefore have a phase difference of zero, are not included in the calculation of PLI. In a study by Stam et al. (2007), PLI and PC of EEG and MEG data were more sensitive than IC to increasing levels of true synchronization in the simulated data, but IC and PLI were less susceptible to spurious correlations in the data due to common sources. In addition, PLI and IC were better able to detect beta band connectivity and uncovered a different spatial pattern of connectivity in the MEG data. IC has also revealed significant changes in the over all resting-state connectivity induced by brain lesions (Marzetti et al., 2007; Guggisberg et al., 2008).

MULTIVARIATE CONNECTIVITY METRICS IN MEG

In contrast to bivariate metrics, which compute relationships between elements in a pair-wise fashion, multivariate metrics are able to model interactions between multiple areas in a single model (see Astolfi et al., 2005). While powerful, computational complexity is an issue when performing a multivariate analysis. While all areas can be modeled simultaneously, the limitation of these methods lies in maintaining the necessary condition that the number of parameters fit in the model does not exceed the number of time points. This is done by considering fewer areas or voxels or by limiting the number of lags the model will analyze. Multivariate autoregressive models (MVAR) can be applied in the time domain, or in the frequency domain, as is the case with partial directed coherence and direct transfer function methods (for examples, see Schelter et al., 2006; Porcaro et al., 2009). Although some of these methods have been demonstrated to be powerful in determining neural networks associated with basic sensory processing (Porcaro et al., 2009) future studies will determine how these metrics can be extended to examinations of impairments in cognitive function in schizophrenia.

DEMONSTRATION: USING IC TO EVALUATE FUNCTIONAL CONNECTIVITY AND COGNITION IN SCHIZOPHRENIA

Bivariate metrics, such as IC, are powerful enough to detect functionally connected networks from MEG data (Nolte et al., 2004; Guggisberg et al., 2008). We have used IC to examine resting-state functional connectivity in 30 clinically-stable, chronically-ill patients with schizophrenia (as diagnosed through the Structured Clinical Interview for DSM-IV) as well as 15 age, gender, and education matched healthy comparison subjects. All participants were assessed with a standard neurocognitive battery of MATRICS-recommended measures (Nuechterlein and Green, 2006) during a separate visit within a 2-week period prior to MEG scanning. Resting state data (eyes closed) was collected over a 4-min period from patients and controls using a 275-channel CTF Omega 2000 whole-head biomagnetometer (VSM MedTech, Coquitlam, BC, Canada) with a sampling rate of 600 Hz. A single epoch (60 s) of artifact-free data was selected specifically for each subject based on the baseline of the MEG sensor data. Sources of oscillating neural activity in the alpha range (~8–12 Hz) were estimated using an adaptive spatial filtering technique (Robinson and Vrba, 1999). IC was computed between each pair of voxels in the MEG timeseries, and then all IC values were Fisher's z-transformed, averaged across all voxels, and spatially normalized to an MNI template (as in Guggisberg et al., 2008). As mentioned in the previous section, this metric (global IC) provides an estimate of functional connectivity at each voxel by averaging across all the connections of that single voxel with the rest of the brain. Given that the characteristics of resting-state MEG data have been shown to be robust indicators of disease state (Georgopoulos et al., 2007), our goal was to evaluate how functional connectivity in both patients with schizophrenia and healthy controls was related to measures of neurocognitive function collected outside of the MEG scan session. Resting-state connectivity maps were correlated with two measures of cognitive function known to be impaired in schizophrenia: a verbal memory task (the Hopkins Verbal Learning Test, HVLT, delayed recall) and a category fluency task. These tasks are known to recruit regions of frontal association cortex involved in language and executive function (Smith et al., 1998; Wager and Smith, 2003; Baldo et al., 2006).

Although performance on HVLT-delayed recall was poorer in the patient group, this difference was not statistically significantly when compared against education-matched controls ($p = 0.07$). However, HVLT-delayed performance was positively

and significantly correlated with IC measures of right dorsolateral pre-frontal cortex (DLPFC; **Figure 7**) only for patients with schizophrenia ($r = 0.51, p < 0.05$, false-discovery rate (FDR) corrected for multiple comparisons) and not healthy comparison subjects ($r = 0.34, p = 0.21$). Such an effect found only in the patient group even when HVLT-delayed scores were not significantly different between the two groups suggests that this relationship between DLPFC connectivity and verbal memory is specific to schizophrenia. Active-state fMRI studies have shown that the functional connections of this region in the right hemisphere, in Brodmann's Area 9 of the middle frontal gyrus, are reduced in schizophrenia during various cognitive tasks such as movement sequencing and continuous performance (Salgado-Pineda et al., 2007; Woodward et al., 2009).

Resting-state functional connectivity scores were also related to performance during a category fluency test, where subjects are required to verbally produce words in a specified category. As in the case of HVLT-delay scores, patient performance was not significantly different from controls ($p = 0.19$). A region of the medial parietal lobe and left DLPFC were positively correlated with performance on this task (**Figure 8**). Category fluency performance was positively correlated with global connectivity of the left medial frontal gyrus, in Brodmann's Area 8 (BA8), across both groups ($p < 0.1$, FDR corrected); a similar trend was seen for the connectivity of the precuneus (Prec; **Figure 8**) only for control subjects ($r^2 = 0.64$, $p < 0.1$ FDR corrected). These data suggest that while BA8 connectivity is related to verbal fluency across groups, an interaction between precuneus connectivity and performance present in controls is absent in patients with schizophrenia. In a recent fMRI study by Schlösser et al. (2009), where patients with schizophrenia are trained to overlearn verbal material, an increase in functional connectivity between left DLPFC and other regions (including right DLPFC, parietal cortex and the cerebellum) were associated with verbal item acquisition. These areas are also known to be underactive in patients during fMRI studies when the task is cognitively demanding (such as the n-back task; Pomarol-Clotet et al., 2008).

CONCLUSION AND FUTURE DIRECTIONS

There is a developing effort in the literature to relate the complexity of early processing in sensory regions to cognitive dysfunction in schizophrenia (Gilbert and Sigman, 2007; Javitt, 2009). Given that early-level sensory processing deficits in schizophrenia (for example, auditory pitch perception or function within the magnocellular pathway in vision) affect "top-down" functions such as emotional discrimination (Leitman et al., 2005; Butler et al., 2009) it is likely that these sensory responses impact higher-level cognitive processing in the disorder. Neuroplasticity-based cognitive training approaches that target auditory processing efficiency have been shown to improve higher-order verbal cognition function and to remediate neurophysiological deficits recorded in MEG (such as M100 attenuation) in patients with schizophrenia (Adcock et al., 2009). Future work using MEG to examine interactions between brain regions – as well as neuroplastic responses in such interactions as a function of cognitive-enhancing interventions – will yield highly useful information for the design of innovative treatments.

There is a considerable degree of cognitive, behavioral and interpersonal complexity to a condition like schizophrenia; therefore, it is reasonable to assume that the neurophysiological framework of the disorder is comprised of functional alterations at multiple levels. MEG is able to interrogate a time scale of neural

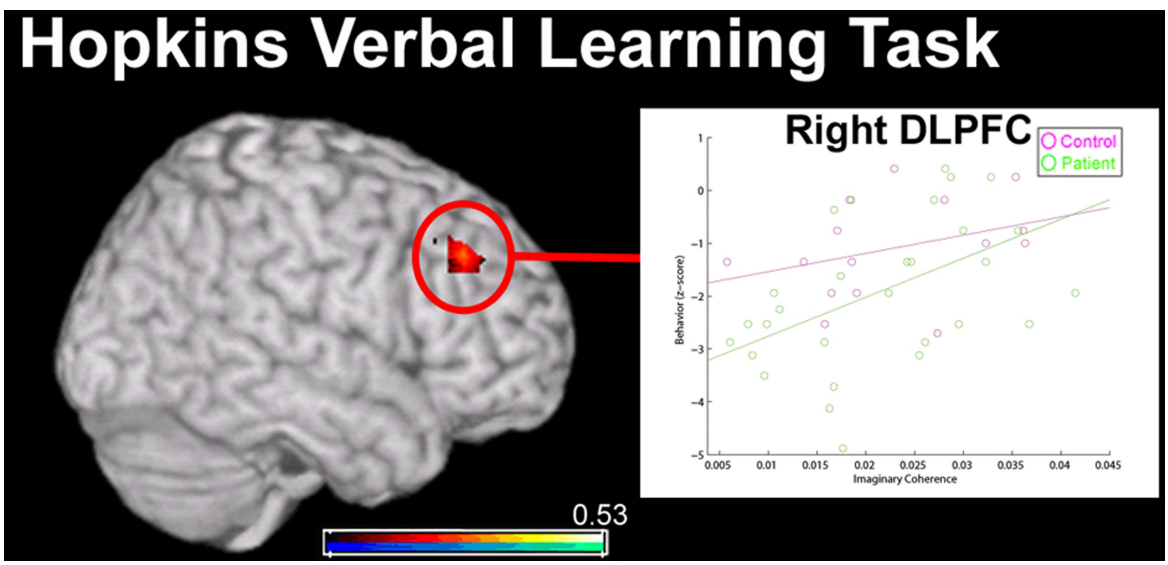

FIGURE 7 | Relationship between MEG resting-state functional connectivity (imaginary coherence) data and performance on the Hopkins Verbal Learning Task (HVLT; delay component) in 15 healthy controls (in pink) and 30 patients with schizophrenia (in green). Global connectivity of a region in right dorsolateral pre-frontal cortex (DLPFC; over the middle frontal gyrus) was positively correlated with HVLT performance (overlay, in red). However, this correlation was only significant for the patient group, indicating that this association between reduced connectivity of right DLPFC and verbal working memory is specific to the disorder. No significant relationship between functional connectivity of any region and performance during immediate recall in the HVLT was identified in either group.

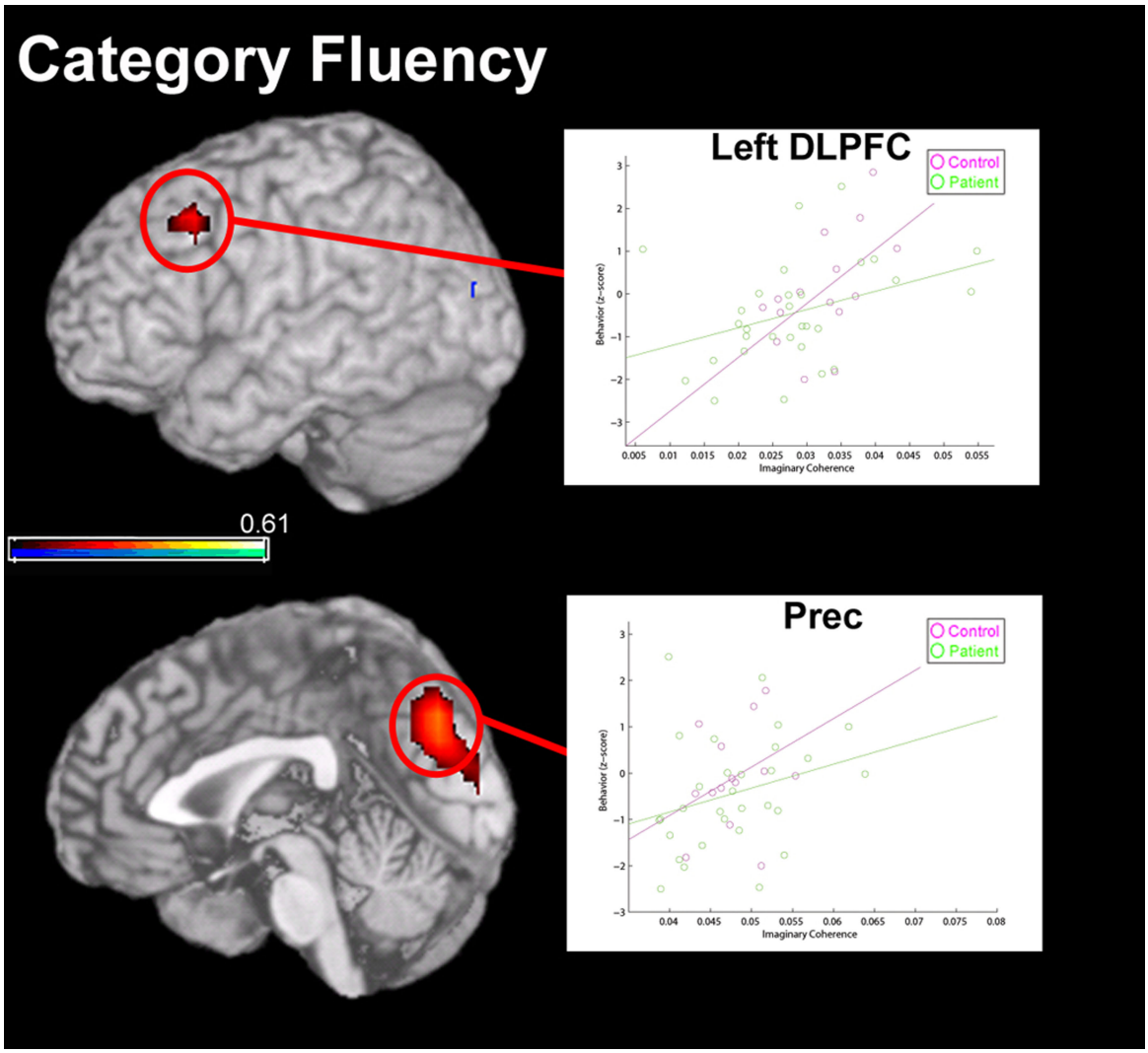

FIGURE 8 | Correlation between global functional connectivity (imaginary coherence) of MEG data at rest with performance on a measure of verbal (Category) fluency. Functional connectivity of two regions were positively correlated (overlay, in red) with performance on this task, including left dorsolateral pre-frontal cortex (DLPFC) and a region of medial parietal cortex, in the precuneus (PreC). In left DLPFC, strong global connectivity was correlated with good performance in both patients and controls. However, in the precuneus, a relationship between global connectivity and Category fluency performance was only significant for the healthy control group.

processing inaccessible to other imaging modalities, and thus serves as a complementary tool for understanding function and connectivity within neural networks in schizophrenia. Promising applications of MEG connectivity in the treatment of the illness are twofold: (1) as a means of characterizing an endophenotype that may predict clinical outcome or response to treatment in prodromal and genetically high-risk patients; and (2) as a means of monitoring changes in brain activity over the course of treatment (see Scherk and Falkai, 2006; Whalley, et al., 2009). It is also possible to capitalize on the spatial and temporal resolution of MEG by combining this data with connectivity information derived from fMRI and DTI (Dale and Halgren, 2001; Stufflebeam et al., 2008; Freeman et al., 2009; Zumer et al., 2009). Ultimately, the goal of this work will be to deepen our understanding of pathophysiology, of effective treatment, and of prevention in this devastating illness.

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Premorbid cognitive deficits in young relatives of schizophrenia patients

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Neurocognitive deficits in schizophrenia (SZ) are thought to be stable trait markers that predate the illness and manifest in relatives of patients. Adolescence is the age of maximum vulnerability to the onset of SZ and may be an opportune "window" to observe neurocognitive impairments close to but prior to the onset of psychosis. We reviewed the extant studies assessing neurocognitive deficits in young relatives at high risk (HR) for SZ and their relation to brain structural alterations. We also provide some additional data pertaining to the relation of these deficits to psychopathology and brain structural alterations from the *Pittsburgh Risk Evaluation Program* (PREP). Cognitive deficits are noted in the HR population, which are more severe in first-degree relatives compared to second-degree relatives and primarily involve psychomotor speed, memory, attention, reasoning, and social-cognition. Reduced general intelligence is also noted, although its relationship to these specific domains is underexplored. Premorbid cognitive deficits may be related to brain structural and functional abnormalities, underlining the neurobiological basis of this illness. Cognitive impairments might predict later emergence of psychopathology in at-risk subjects and may be targets of early remediation and preventive strategies. Although evidence for neurocognitive deficits in young relatives abounds, further studies on their structural underpinnings and on their candidate status as endophenotypes are needed.

Keywords: schizophrenia, neurocognition, premorbid, relatives, MRI

INTRODUCTION

Schizophrenia (SZ) was originally described over a century ago with the earlier name "dementia praecox," which literally means "cognitive decline with onset in youth." Cognitive impairment is *highly prevalent* in patients with SZ as determined by the majority of patients who show cognitive decrement relative to parental education (Keefe et al., 2005) or to their own estimate of premorbid intelligence measured by single word identification (Kremen et al., 1995). Meta-analyses show that cognitive impairment distinguishes patients with SZ from healthy comparison subjects to a *robust* degree (i.e., an effect size of approximately one with approximately one standard deviation); these deficits are apparent at the first episode and roughly are equal to those observed in chronic cases (Mesholam-Gately et al., 2009). Average effect sizes for cognitive impairments in SZ are about twice as large as those obtained in structured magnetic resonance imaging studies (Heinrichs, 2005). Cognitive impairment is a *stable*, *trait-related* aspect of SZ, being present in the early phase of the illness and persisting during the long-term course (Rund, 1998). Cognitive impairment is a *predictor* of social and vocational outcome as evaluated longitudinally (Green et al., 2004). Recent studies suggest that social cognition may have a particularly strong relation to functional outcome (Green et al., 2004). Finally, cognitive impairment may differ to some extent between SZ and other psychiatric disorders (MacDonald et al., 2005). Cognitive deficits in patients with SZ are generally more severe and pervasive compared to patients with psychotic and non-psychotic affective disorders (Seidman et al., 2002a; Hill et al., 2004a). All of the above observations firmly point to cognitive deficits being a core feature of SZ and clearly a key path toward understanding the etiopathology of this illness.

Genetic factors are the best established etiological determinants of SZ (Keshavan et al., 2005) as suggested by a heritability of 0.41–0.87 (Cannon et al., 1998). The risk of SZ is proportional to genetic dose (number of affected relatives and relatedness with the proband). This suggests that studies of relatives at genetic high-risk are a very valuable approach to elucidate the genetic underpinnings of this illness. Offspring of patients have a 10-to 15-fold increase in risk of developing the illness. Having two parents with SZ increases the risk to about 40% (Keshavan et al., 2004). While studies of unaffected relatives of SZ patients help us understand the genetic underpinnings of this illness, all such relatives may not necessarily be at high-risk; studies of young relatives who are within, or younger than the age range of risk for SZ are more likely to illuminate neurocognitive indicators of risk. The view that SZ is a neurodevelopmental disorder (Feinberg, 1982; Murray and Lewis, 1987; Weinberger, 1987; Keshavan et al., 2006) suggests that neurocognitive and neurobiological alterations may be detectable in the *premorbid* phase before the typical onset of the features of the illness (e.g., psychosis) during childhood, adolescence, or early

adulthood. These alterations may also represent endophenotypes (i.e. markers intermediate between phenotypic manifestations of the disease and the genotype) (Gottesman and Gould, 2003).

In this paper, we review studies that have examined various cognitive domains including attention, learning and memory, general intelligence, social-cognition, speed of processing and executive-function (Henry and Crawford, 2005) in unaffected young relatives presumed to be at high genetic risk. We did an extensive PubMed search using keywords "schizophrenia", "relatives" and "cognition." In particular, several high-risk studies conducted over the last three decades were reviewed (**Table 1**). We also summarize findings from our ongoing studies related to neurocognition, as well as provide some additional data on the nature of cognitive deficits and their relation to neurobiological alterations as well as the dose of familial risk (first vs. second-degree relatives) in young relatives at risk for SZ.

NATURE OF NEUROCOGNITIVE DEFICITS IN YOUNG RELATIVES AT RISK FOR SZ

There are prominent impairments in SZ in several domains of cognition, including psychomotor speed, memory, attention, reasoning, and social cognition (**Table 1**). These may be easily remembered by the mnemonic *SMART* [Speed of processing, Memory, Attention, Reasoning and Tact (or social cognition)]. Studies have suggested some inter-correlation between cognitive performance on these domains, although there is no clear consensus regards the degree of shared variance across domains. Studies have shown both significant (Dodrill, 1997) and non-significant correlations between these domains (Nuechterlein et al., 2008) in patients with SZ. A common "general intelligence" factor, correlating with all domains may explain the lack of independence of cognitive performance on these domains. Evidence suggests correlation of IQ (an index of general intelligence) with performance across domains in SZ patients (Bell and Roper, 1998; Tremont et al., 1998; Horton, 1999; Jung et al., 2000; Kremen et al., 2008) and may represent this common general intelligence factor. Alternatively, the inter-dependence of specific cognitive domains could be due to similarities across the different neuropsychological tests used to assess different domains (Larrabee, 2000). Although IQ deficits generally share variance with specific cognitive deficits, deficits in some domains such as speed of processing and verbal memory have been found to be independent of the IQ deficits. It is therefore unclear if domain-specific deficits can be fully accounted for by a super-ordinate factor like general intelligence.

SPEED OF PROCESSING

This domain measures cognitive efficiency and involves the ability to automatically and fluently perform relatively easy or repetitive cognitive tasks. Shakow (1963) originally described this deficit in SZ studying reaction time slowing. Speed of processing has been posited as a predictor of global functioning, autonomy, self care and hence of illness outcome and quality of living (Sánchez et al., 2009). Reaction time, an indicator of speed of processing, is increased in relatives of patients (Birkett et al., 2007). Young relatives at risk for SZ have reduced processing speed even after controlling for IQ as shown by the Edinburgh High-Risk Study (EHRS) ($p = 0.044$) (Byrne et al., 2003; Cunningham Owens and Johnstone, 2006; O'Connor et al., 2009), as well as our studies which will be described later. These deficits might be state-independent given that psychotic symptoms do not alter the severity of speed of processing deficits in patients (O'Connor et al., 2009). Evidence suggests that processing speed may depend on testing conditions. In a study with varying cognitive processing loads, while the fastest reaction times (that happen during low-cognitive load tasks) were not increased in relatives (Birkett et al., 2007), mean reaction time was slower, suggesting slower reaction times during high-cognitive-load tasks. Slowed performance on the various psychomotor measures has been shown to be independent of medication (Morrens et al., 2007). Speed of processing has also been found to predict negative symptoms and impaired functional outcomes (Niendam et al., 2006; Morrens et al., 2007).

A genetic-load effect is noted with performance of relatives being intermediate between that of healthy controls and patients on this domain (Birkett et al., 2007; Gur et al., 2007b; Bertisch et al., 2009). Reaction time has been proposed as a putative endophenotype of the illness (Wang et al., 2007). However, a study showed that both patients with and without reaction time deficits on the Continuous Performance Test (CPT) have relatives showing these deficits (Birkett et al., 2007). Thus, the candidacy of reaction time deficits as an endophenotype, as well as their role as premorbid vulnerability indicators deserve further consideration.

MEMORY

Working memory (WM) involves holding information online for brief periods of time, and typically involves processes like information manipulation, maintenance and monitoring in verbal, visual and spatial domains (Kellogg et al., 2007). Maintenance involves retaining information in a sequential manner, manipulation deals with rearrangement of the information sequence while monitoring checks and updates the contents of WM to determine the next step in a sequential task. WM in all subsystems is impaired in first episode patients (Zanello et al., 2009) and unaffected first degree relatives (Conklin et al., 2005; Saperstein et al., 2006; Horan et al., 2008). Relatives of SZ patients perform poorly on spatial WM (Awh et al., 1998; Saperstein et al., 2006) and spatial memory capacity (O'Connor et al., 2009). Several studies report impairments in verbal, spatial and object WM domains with a graded pattern of impairment; deficits in patients > relatives > controls are observed for verbal WM (Niendam et al., 2003; Conklin et al., 2005). Deficits in WM appear to correlate with negative symptoms (Chkonia and Tsverava, 2007). Impaired WM has been proposed as a putative endophenotype for SZ (Niendam et al., 2003).

Verbal declarative or long-term memory is significantly reduced in patients (Chkonia and Tsverava, 2007), is associated with earlier disease onset, is related to social functioning and negative symptoms (Niendam et al., 2006), and is proposed to be a predictor of later SZ in high-risk individuals (Niemi et al., 2003; Groom et al., 2007) (**Table 1**). However, a study reported no verbal-memory deficits in high-risk offspring after controlling for education (Chkonia and Tsverava, 2007). In the EHRS, deficits in Rey's auditory verbal learning test predicted later SZ but deficits in Rivermead Behavioral Memory Test did not (Byrne et al., 1999, 2003; Cosway et al., 2000; Johnstone et al., 2002, 2005; Whyte et al., 2006; Whalley et al., 2007). The New York High-Risk Project (NYHRP) reported that verbal

Table 1 | Findings in cognitive domains in high-risk relatives.

Study/author	Design	Groups and sample size	Major findings
SPEED OF PROCESSING			
EHRS	18-m intervals for 5 y f/u	HR = 163, C = 36	Impaired speed of processing
NCPP	0, 4, 8 m, 1, 4, 7 y f/u	S = 32, HR = 25, HC = 201	Deficits in coding subtest ($p = 0.03$)
MEMORY			
EHRS	18-m intervals for 5 y f/u	HR = 163, C = 36	Deficits in spatial memory capacity
PREP	3 y f/u	HR = 81, C = 80	Reduced spatial working memory
HHAHRS	Cross sectional	HR SZ = 73, HR Aff = 18, C = 84	Reduced verbal, visual-spatial and working memory
Delawalla et al. (2006)	Cross sectional	S = 27, HR = 31, HC = 39, HC sib = 42	Deficits in working memory
EHRS	18-m intervals for 5 y f/u	HR = 163, C = 36	Deficits in verbal memory predicted future schizophrenia
NYHRP	6 assessments, first 9 y, latest 30 y f/u	Phase A: HR = 84, HR aff = 67, C = 136 Phase B: HR = 46, HR aff = 39, C = 65	Verbal short-term memory predicted schizophrenia
NCPP	0, 4, 8 m, 1, 4, 7 y f/u	HR = 54, HC = 72	Verbal memory deficits with significant gender interaction
EHRS	18-m intervals for 5 y f/u	HR = 163, C = 36	Deficits in visual memory
ATTENTION			
IHRS	8–15, 14–21, 23–30, 31–40 y f/u	HR = 50, C = 50	Poor attentional skills predicted later SZ
JIDS	0, 3, 14 d, 4, 8, 12 m, 7–14, 14–21 y f/u	HR = 29, other = 30, C = 27	Attentional dysfunction, measured as part of global neurobehavioral functioning
NYHRP	6 assessments, first 9 y, latest 30 y f/u	Phase A: HR = 84, HR aff = 67, C = 136 Phase B: HR = 46, HR aff = 39, C = 65	Attention deficits predicted social outcome and later SZ
SBHRP	7–15, 10–18, >18 y f/u	HR = 80, HR mdd = 154, HR BP = 134, C = 176	Impaired perceptual sensitivity (d')
PREP	3 y f/u	HR = 81, C = 80	Impaired sustained attention
REASONING AND EXECUTIVE FUNCTION			
Franke et al. (1992)	Cross sectional	S = 73, HR = 61, HC = 35	More perseverative errors and relatively normal non-perseverative errors
EHRS	18-m intervals for 5 y f/u	HR = 163, C = 36	Deficits in response inhibition
Ma et al. (2007)	Cross sectional	S = 207, HR = 322, C = 133	Poor performance on perseverative errors
Klemm et al. (2006)	Cross sectional	HR = 32, HC = 32	Poor performance on completed categories and perseverative errors
TACT OR SOCIAL COGNITION			
JIDS	0, 3, 14 d, 4, 8, 12 m, 7–14, 14–21 y f/u	HR = 29, other = 30, C = 27	Impaired social competence
NYHRP	6 assessments, first 9 y, latest 30 y f/u	Phase A: HR = 84, HR aff = 67, C = 136 Phase B: HR = 46, HR aff = 39, C = 65	Impaired social competence
EUP	0–5,1–6, 2–7 y, studied three times 1 y apart f/u	HR SZ = 61, HR mdd = 33, C = 33	Impaired social competence
Eack and Mermon (2009)	Cross sectional	HR = 70, HC = 63	Emotion recognition deficits associated with prodromal symptoms
Bediou et al. (2007)	Cross sectional	S = 40, HR = 30, HC = 26	Impaired emotion recognition
EHRS	18-m intervals for 5y f/u	HR = 163, C = 36	Deficits in theory of mind tasks
GENERAL INTELLIGENCE			
EHRS	18-m intervals for 5 y f/u	HR = 163, C = 36	Deficits in all measures of IQ (full scale, verbal and performance IQ) and poor IQ predicted future schizophrenia

(Continued)

Table 1 | ***Continued***

Study/author	Design	Groups and sample size	Major findings
NCPP-B and NCPP-P	0, 4, 8 m, 1, 4, 7 y f/u	HR SZ = 118,HR aff = 126, C = 165	Deficits in IQ, lower premorbid IQ associated with genetic vulnerability to SZ
RLS	0, 4 m, 1, 2.5, 4 y f/u	HR SZ = 29, HR other = 98, C = 57	No significant IQ deficits
HHAHRS	Cross sectional	HR Sz = 73, HR Aff = 18, C = 84	Reduced verbal ability (d = 0.73)
SLRRP	7, 10, 13, 16, 19, 22, >25 y f/u	HR = 100, HR aff = 60, C = 130	Temporal progression in IQ deficits and a time by parental diagnosis interaction on verbal IQ
NYHRP	6 assessments, first 9 y, latest 30 y	Phase A: HR = 84, HR aff = 67, C = 136 Phase B: HR = 46, HR aff = 39, C = 65	No temporal progression in IQ deficits and could not predict schizophrenia

D, Days; m, months; y, years; f/u, follow-up; aff, affective psychosis; C, control group; de, depression; HR, High-Risk group; HC sib, siblings of healthy controls; mdd, major depressive disorder; other, other mental disorder; HR other, high risk for other disorders; pd, personality disorder; S, schizophrenia; HR BP, High risk for bipolar disorder; HR SZ, high risk for schizophrenia; HR aff, high risk for affective psychoses; EHRS, Edinburgh High Risk Study (Byrne et al., 1999, 2003; Cosway et al., 2000; Johnstone et al., 2002, 2005; Marjoram et al., 2006; Owens and Johnstone, 2006; Whyte et al., 2006; Whalley et al., 2007; O'Connor et al., 2009); PREP, Pittsburgh Risk Evaluation Program (Keshavan et al., 2005); HHAHRS, Harvard and Hillside Adolescent High Risk Study (Seidman et al., 2006); NCPP, National Collaborative Perinatal Project (P-Providence, B-Boston) (Kremen et al., 1997; Goldstein et al., 2000; Niendam et al., 2003); NYHRP, New York High Risk Project (Freedman et al., 1998; Cornblatt et al., 1999; Erlenmeyer-Kimling et al., 2000); JIDS, Jerusalem Infant Development Study (Marcus et al., 1987; Hans et al., 1999); IHRS, Israeli High Risk Study (Marcus et al., 1987; Mirsky et al., 1995); EUP, Emory University Project (Goodman, 1987); SLRRP, St. Louis Risk Research Project (Worland et al., 1982); RLS, The Rochester Longitudinal Study (Sameroff et al., 1987); SBHRP, Stony Brook High Risk Project (Weintraub, 1987; Franke et al., 1992; Delawalla et al., 2006; Klemm et al., 2006; Bediou et al., 2007; Ma et al., 2007; Eack and Mermon, 2009).

memory deficits predict 83% of high-risk subjects who subsequently received a diagnosis of SZ. The Harvard and Hillside adolescent high-risk study (Seidman et al., 2006) showed that verbal memory impairment may have promise as a premorbid predictive marker in those at genetic risk for the illness, but further investigation is needed into confounding mediator factors such as affective symptomatology, education and environmental factors in these deficits. Another multi-site study (The Consortium on the Genetics of Schizophrenia) has proposed verbal WM deficits to be putative inherited endophenotypes of SZ (Greenwood et al., 2007; Horan et al., 2008). In general, verbal memory has been shown to be one of the most robust deficits in studies of relatives.

Visual memory has been studied less frequently than verbal memory in patients, and impairments in the visual domain among family members appear to be somewhat less severe than in the verbal domain (Snitz et al., 2006). A study reported verbal recall deficits over short and long delays in both patients and relatives of patients but visual recall deficits only in patients (Heinrichs and Zakzanis, 1998; Whyte et al., 2005; Delawalla et al., 2006). Visual recall deficits have been thought to be state dependent while verbal memory deficits may be heritable stable trait markers (Skelley et al., 2008). Visio-spatial memory deficits in relatives correlate with their proximity to probands (genetic loading) (Robles et al., 2008). Also, visual recall deficits in delayed recognition tasks have been observed in high-risk relatives (Byrne et al., 1999).

ATTENTION

Attention involves the appropriate allocation of processing resources to relevant stimuli, and includes sub-processes like sustained attention and selective attention. A frequently used test to assess attention-performance is the CPT. Several CPT versions vary with regards to modality (auditory or visual), type of stimulus (letters, numbers, colors, or geometric forms), and nature of the task (Miranda et al., 2008). Attentional abnormalities have been well documented in SZ; attentional deficits are associated with negative and disorganized symptoms and persist despite treatment. Impaired sustained attention indexed by perceptual sensitivity (d′) in the CPT task strongly discriminates high-risk relatives from healthy controls (Erlenmeyer-Kimling et al., 2000); attention deficits are consistent, temporally stable, and independent of environmental factors or onset of psychotic symptoms (Freedman et al., 1998; Cornblatt et al., 1999; Erlenmeyer-Kimling et al., 2000). Attention deficits predicted more than half (58%) of the high-risk offspring who developed SZ in their future (Erlenmeyer-Kimling et al., 2000). Measures of attention deviance predicted social outcomes while poor neurobehavioral functioning predicted future SZ spectrum disorders (Marcus et al., 1987; Erlenmeyer-Kimling et al., 2000). Attention deficits have been observed in unaffected relatives in the prodromal as well as premorbid phases and have been considered as "endophenotypes" for later emergence of SZ (Cornblatt and Malhotra, 2001), using poor attentional performance as a marker of vulnerability to SZ could provide a valuable measure of genetic risk.

REASONING AND EXECUTIVE FUNCTION

Executive functions refer to cognitive processes that bear specific tasks related to problem solving. Abstraction (extracting a common feature from various perceptions), reasoning, set shifting (ability to modify ongoing behavior in response to changing goals or environmental input), and error monitoring are critical aspects of executive function. Perseverative and non-perseverative errors on the *Wisconsin Card Sorting Test* (WCST) are indicators of deficits in cognitive set shifting and generalized reasoning, respectively (Franke et al., 1992; Gur et al., 2007c). Relatives of SZ patients show higher perseverative errors but relatively normal non-perseverative errors than controls, suggesting cognitive set shifting to be a vulnerability marker of the illness. Additionally, patients have deficits in non-perseverative errors indicating these to be state dependent; poorer performance on reasoning and problem solving is associated with reduced global functioning (Niendam et al., 2006). By factor analysis in first degree relatives, perseverative errors, set-shifting difficulties, and

idiosyncratic sorting were identified as orthogonal (uncorrelated) dimensions assessed by the WCST (Koren et al., 1998). In young high-risk relatives of SZ patients, EHRS found deficits in executive function (Johnstone et al., 2002; Byrne et al., 2003), while another study displayed poor performance on WCST in relatives of patients having a family history of SZ compared to relatives of patients without a family history of SZ (Birkett et al., 2008). Some studies have been equivocal (Stratta et al., 1997), suggesting further investigation.

SOCIAL COGNITION

Social cognition involves faculties allowing tactful and socially appropriate behavior that involve affect perception, emotion regulation, and the ability to infer other people's mental states (Theory of Mind). These functions are reported to be compromised in individuals with SZ (Kindermann et al., 1997; Brune, 2005). Impairments in social cognition are only partly correlated with and largely independent of neurocognitive dysfunction (Corrigan et al., 1994; Sergi et al., 2007), and may underlie symptoms of SZ and disability (Bentall et al., 2001; Sergi et al., 2006). Studies have shown that many of these domains of cognitive impairment are stable over time and are present after the cessation of schizophrenic symptoms (Rund, 1998; Hill et al., 2004b).

Social cognitive deficits may have predictive value for later SZ (Niendam et al., 2006, 2007b; Simon et al., 2006; Calkins et al., 2007; Matsumoto et al., 2007; Suzuki et al., 2007; Yui et al., 2007; Chung et al., 2008; Fornito et al., 2008; Meisenzahl et al., 2008; Muñoz Maniega et al., 2008; Shim et al., 2008; O'Brien et al., 2009; Sun et al., 2009). A large body of evidence shows social cognition aberrations to be the predominant cognitive deficit in the prodrome, a phase that often progresses to psychotic disorder (Moller and Husby, 2000; Cohen et al., 2006; Niendam et al., 2006, 2007a; Simon et al., 2006; Cannon et al., 2008; Chung et al., 2008). Social dysfunction is a predictor of future positive symptoms (Moller and Husby, 2000; Cohen et al., 2006; Niendam et al., 2006; Cannon et al., 2008) and influences prodromal morbidity and functioning more than other neurocognitive deficits (Niendam et al., 2006, 2007b; Simon et al., 2006; Calkins et al., 2007; Shim et al., 2008; O'Brien et al., 2009). Structural alterations in regions mediating social cognition (McDonald et al., 2004; Braff and Light, 2005; Bender et al., 2007; Braff et al., 2007; Gur et al., 2007b,c; Keshavan et al., 2007; Prasad and Keshavan, 2008; Kallimani et al., 2009) might therefore be promising predictors of SZ.

Unaffected relatives of patients show deficits in emotion recognition (Kee et al., 2004; Bediou et al., 2007; Eack and Mermon, 2009), and theory of mind tasks (Anselmetti et al., 2009). A study on siblings of SZ patients (Leppanen et al., 2008) demonstrated significant performance deficits in the recognition of facial anger. Recently, one study (Addington et al., 2008) found that individuals clinically at high risk (HR) for developing SZ (i.e., those with prodromal symptoms) performed as poorly as first episode patients on an emotion identification task. Theory of mind deficits also have been shown to be compromised in relatives and together with emotion perception may predict functioning in the community (Irani et al., 2006; Marjoram et al., 2006; Pijnenborg et al., 2009). As reviewed in Phillips and Seidman (2008), emotion perception deficits in relatives are consistently present, as well as social anhedonia and negative affect. Some studies have found high-risk offspring to have poor social competence (Goodman, 1987; Marcus et al., 1987; Dworkin et al., 1993).

VERBAL FLUENCY

Language related cognitive deficits, verbal memory (Goldberg et al., 1998; Riley et al., 2000), verbal fluency (Goldberg et al., 1998; Riley et al., 2000), semantic memory (Lorente-Rovira et al., 2007), comprehension (Condray et al., 2002), and receptive language (Condray et al., 2002) are found to be deficient in patients with SZ and are also present in at-risk children (Keefe et al., 1994; Chen et al., 2000; Weiser et al., 2007). Category verbal fluency indexes semantic memory, lexical access, and executive function while letter fluency may index psychomotor speed (Benton and Hamscher, 1978). Although verbal fluency is shown to be altered in relatives of SZ patients (Bhojraj et al., 2009), few studies have assessed young relatives (Broome et al., 2009). A recent meta-analysis revealed a large effect size (0.68) in category fluency (Snitz et al., 2006). Verbal fluency may be significantly correlated with intelligence (Gilvarry et al., 2001); another study reported deficits in verbal fluency and executive function among relatives of SZ patients (Keefe et al., 1994). The possibility of verbal fluency deficits in young relatives was assessed by the *Pittsburgh High-Risk Study* (see below) which found significant deficits at the baseline assessment.

GENERAL INTELLIGENCE

Intelligence deficits in relatives at risk for SZ are equivocal with studies both showing (Mednick and Schulsinger, 1968; Rieder et al., 1977; Dworkin et al., 1993; Byrne et al., 1999; Goldstein et al., 2000) and not showing significant IQ deficits (Sameroff et al., 1987). IQ deficits tend to progress with time as evidenced by some studies (Worland et al., 1982) while others did not find such a pattern (Goodman, 1987; Dworkin et al., 1993). Some studies with HR offspring bearing IQ deficits predicted adult SZ (Cosway et al., 2000) while others could not (Dworkin et al., 1993). A study reported low social status and severity of maternal illness to be strong predictors of low IQ in offspring of patients (Sameroff et al., 1993). Worland et al. (1982) reported a time by parental diagnosis interaction on verbal IQ among HR offspring, children of mothers with SZ showed more deficits than children of fathers with SZ during a 16-year follow-up, and also children of SZ parents had the lowest stability on IQ scores. The question of whether the liability to SZ is mainly related to a generalized intellectual defect or whether there exists unique cognitive domains with selectively more prominent impairments remains unclear (Woodberry et al., 2008).

NEUROBIOLOGY OF COGNITIVE DEFICITS IN HR RELATIVES

SZ patients show enduring structural gray matter volumetric deficits of the subcortical regions (Ellison-Wright et al., 2008), medial-temporal, cingulate, prefrontal temporal, and parietal cortices (Shenton et al., 2001). These alterations may be heritable and have been posited as stable trait markers or endophenotypes of SZ (Keshavan et al., 2007; Prasad and Keshavan, 2008). As structural alterations may reflect genetic liability to SZ, brain regions altered in patients may also be altered in their relatives (Keshavan et al., 2007; Prasad and Keshavan, 2008). High-risk relatives show alterations of amygdalae, hippocampus (Keshavan et al., 1997, 2002;

Seidman et al., 1997, 1999, 2002b; O'Driscoll et al., 2001; Lawrie et al., 2002; Boos et al., 2007; Lawrie et al., 2008), thalami (Seidman et al., 1999), basal ganglia (Staal et al., 1998), anterior cingulate gyros (Diwadkar et al., 2006; Fornito et al., 2008), and ventricular enlargement (Boos et al., 2007; Lawrie et al., 2008). HR subjects have been reported to show structural alterations in white matter: reduced levels of FA (Fractional Anisotropy – an indicator of white matter integrity) (Hoptman et al., 2008) in anterior limb of internal capsule (Muñoz Maniega et al., 2008) and in bilateral cingulate and angular gyri (Hoptman et al., 2008) but relatively increased orbitofrontal white matter volumes (Fan et al., 2008). Deficits in left posterior cingulate, right inferior parietal, orbitofrontal cortex, and right middle frontal agree with results from the EHRS (Job et al., 2005) which found an exaggerated longitudinal volume decline in these regions in relatives using voxel based approaches. A left > right decrement of the hippocampal amygdalar complex (Keshavan et al., 2002; Tanskanen et al., 2005) in relatives of patients is also reported (Seidman et al., 2002b). The left parahippocampal gyrus is noted to be altered in those at genetic risk (Seidman et al., 2003). As reviewed earlier, studies in young relatives of SZ patients have found deficits (Sitskoorn et al., 2004; Heydebrand, 2006; Snitz et al., 2006; Gur et al., 2007c) in executive-function (Diwadkar et al., 2001), working-memory, attention (Vanderzeypen et al., 2003; Klemm et al., 2006; Lencz et al., 2006; Seidman et al., 2006; Schubert and McNeil, 2007), language (Byrne et al., 1999; Cosway et al., 2000; Erlenmeyer-Kimling, 2001; Schubert and McNeil, 2007; Thermenos et al., 2007), speed of processing (Konrad et al., 2008) and social cognition (Irani et al., 2006; Gur et al., 2007c; Baas et al., 2008; Mazza et al., 2008). It is proposed that speed of processing (reaction time) depends on nerve conduction velocity which is in turn based on the myelination of white matter fibers (Begré et al., 2008). Subjects at risk for SZ have altered white matter volumes, and may lead to slower reaction time (Konrad et al., 2008). Preliminary studies show that presence of genetic polymorphisms affecting the integrity of white-matter tracts may correlate with reaction-time deficits (McIntosh et al., 2007).

The amygdalae, hippocampi, and orbito and medial prefrontal regions mediate social-cognition (Bechara et al., 2003; Britton et al., 2006; Tsukiura and Cabeza, 2008). The inferior parietal lobule (Hunter et al., 2003), and the inferior frontal cortex (Papathanassiou et al., 2000; Maess et al., 2006; Kawasaki et al., 2008) perform language processing while the thalamus, caudate-nucleus (Salgado-Pineda et al., 2003; Gur et al., 2007a), middle frontal gyrus, and superior parietal cortex (Wager and Smith, 2003) have been shown to mediate attention, working-memory, and executive function (Seidman et al., 1994; Menon et al., 2001; Shad et al., 2004; Owen et al., 2005). Frontal release signs, indices of prefrontal pathology are correlated with executive function and attention (Hyde et al., 2007).

Premorbid cognitive deficits may map onto observed structural deficits in brain regions mediating corresponding cognitions. Relations between cognitive deficits and brain structural alterations in high-risk relatives have not been systematically examined. If such relations are established, cognitive and brain structural deficits, both considered to be endophenotypes of SZ, might be more parsimoniously explained by the "extended endophenotype" concept (Kippenhan et al., 2005).

NEUROCOGNITIVE DEFICITS IN YOUNG HR RELATIVES: FINDINGS FROM THE *PITTSBURGH HIGH-RISK STUDY*

In an ongoing longitudinal study, the Pittsburgh Risk Evaluation Program (PREP), we assess young (10–25 years) first- and second-degree relatives of SZ probands and healthy controls. The participants were identified at the Western Psychiatric Institute and Clinic (WPIC), Pittsburgh or related clinical sites. Young HR relatives were recruited by first approaching patients with SZ with eligible relatives in our outpatient clinical services and via advertisements in community locations. Participants were included if they had a first or second degree relative with SZ or schizoaffective disorder, had an IQ ≥ 80, did not have any lifetime evidence of psychotic disorders, antipsychotic medication exposure, history of substance use, and neurological or medical condition. Age and gender matched healthy controls were recruited from the same community neighborhoods as HR subjects. The study design, demographic, and clinical characteristics of these subjects have been described elsewhere (Keshavan et al., 2008). We report herein summary observations in key neurocognitive domains and their neuroimaging correlates.

Previously published findings from the PREP study involve deficits in memory, attention, verbal fluency, executive function, social cognition, and general intelligence. High-risk offspring performed poorer compared to controls on spatial WM, sustained attention, category verbal fluency (Eack et al., 2008), executive function (Keshavan et al., 2004, 2005; Eack et al., 2008), and general intelligence (Eack et al., 2008). Social cognition deficits in facial emotion recognition were also noted (Eack and Mermon, 2009). Relatives were found to over-attribute negative valence to neutral faces and took longer to identify neutral faces. These deficits were independent of other neurocognitive dysfunction and correlated with positive symptoms and general psychopathology scores (Keshavan et al., 2004). Compared to healthy controls, relatives of SZ patients were more prone to develop attention deficit hyperkinetic disorder (Keshavan et al., 2003) and schizotypal personality traits. Using a multivariate psychobiological prediction model comprised of neuroimaging, neurocognitive, and psychosis proneness measures, these variables together predicted 71% chance to develop psychopathology, in contrast to individuals not identified to develop psychopathology by the model who only had a 17% chance of developing psychopathology (Eack et al., 2008). In this review, we provide additional data on (a) neurocognitive findings and their familial dose effects and (b) brain structural correlates of neurocognitive deficits in young relatives at risk for SZ.

NEUROCOGNITIVE DEFICITS AND GENETIC DOSE EFFECTS

Neurocognitive scores (measured in parentheses) were collected from a neuropsychological battery including IQ (Wechsler Abbreviated Scale of Intelligence; Wechsler, 1999); WM (Cogtest Spatial Working Memory Test; distance median after a 12-s delay; Cogtest, 2009); executive functioning (Wisconsin Card Sorting Test perseverative error scores; Heaton et al., 1993); attention (Continuous Performance Test, IP version visual *d prime*; Cornblatt et al., 1988); and verbal fluency (Benton and Hamscher total correct from the category/letter fluency task; Benton and Hamscher, 1978).

Table 2 | Neurocognitive findings in young relatives of schizophrenia patients in the Pittsburgh High-Risk Study.

Cognitive domain	Test	Sample size	Healthy controls, mean, SD	HR subjects, mean, SD	Controls vs. HR subjects, *F* (*p* value)	Effect size, partial eta square
Psychomotor speed	Go reaction time (Go-no-go test)	HC = 56, HR = 86	426.8, 0.82	488.9, 0.94	18.25 (0.000)	0.12
Sustained attention	CPT-IP visual d′	HC = 85, HR = 118	1.63, 0.82	1.17, 0.94	9.76 (0.002)	0.05
Verbal fluency	Letter and category	HC = 47, HR = 69	83.2, 20.7	69.1, 18.4	11.67 (0.001)	0.09
Spatial working memory	Delayed recognition task (12 s delay)	HC = 58, HR = 66	55.8, 22.3	67.0, 30.1	3.46 (0.065)	0.03
Executive Function	Wisconsin Card Sort Test, perseverative errors	HC = 96, HR = 122	11.94, 5.4	12.0, 6.15	6.18 (0.433)	0.00

HR, first-degree relatives of patients, HC, healthy controls, CPT-IP, Continuous Performance Test, Identical Pairs version.

Table 2 denotes deficits seen in first- and second-degree relatives (HR) compared to HC controlling for age at baseline assessment of the PREP study. Significant deficits were noted in HR in IQ ($p < 0.000$). Higher order cognitive domains like executive function and spatial-WM (Nuechterlein et al., 2008) were not as prominently affected in HR as were simpler domains such as psychomotor speed, sustained attention, and verbal fluency. Deficits in both attention and spatial WM were attenuated and those in verbal fluency lost significance after controlling for psychomotor speed, suggesting that higher order cognitive deficits may be mediated by deficits in hierarchically more basic cognitive processes such as speed of processing (Nuechterlein et al., 2004). We assessed familial-loading effects by comparing groups of first-degree relatives ($n = 122$), second-degree relatives ($n = 23$) and healthy controls ($n = 109$) using ANCOVA models. Familial-loading effects were seen at $p < 0.05$ for psychomotor speed ($F = 5.89$, $p = 0.043$), executive-function ($F = 4.56$, $p = 0.05$) and verbal-fluency ($F = 3.91$ $p = 0.078$) with first-degree relatives performing poorer than second-degree relatives on all domains except WM. **Figure 1** shows that first-degree relatives have the more prominent deficits, while second-degree relatives have impairment intermediate to that of first-degree relatives and healthy controls in all domains except WM. No moderating effects of gender on the main effect of study group (HR vs. HC) were noted.

As the exact relation of IQ deficits with domain specific deficits is unclear, we conducted parallel analyses controlling, as well as not controlling for IQ. Deficits in sustained attention ($F = 5.1$, $p = 0.025$), speed of processing ($F = 5.2$, $p = 0.023$), and verbal fluency (6.2, $p = 0.011$) in relatives survived controlling for IQ. All neurocognitive scores were significantly correlated with IQ (r ranging from 0.30 to 0.43). Studies in patients have shown most neurocognitive deficits, except for psychomotor speed and verbal memory, to be mediated by a latent "cognitive ability factor" (Weickert et al., 2000; Dickinson et al., 2008). This agrees with findings of attention and verbal fluency deficits but not psychomotor speed deficits losing significance after controlling for IQ in the PREP study. A latent cognitive ability factor as underpinning all neurocognitive deficits is debatable as the latent factor was revealed using a correlation method in a cross-sectional design (Dodrill, 1997, 1999; Bell and Roper, 1998; Tremont et al., 1998; Horton, 1999; Jung and Haier, 2007; Dickinson et al., 2008). Longitudinal studies have shown cognitive deficits to precede generalized cognitive deficits like IQ (Weickert et al., 2000). Controlling for IQ when assessing cognitive deficits may be unnecessarily conservative, especially given the equivocal evidence about the role of IQ in cognitive deficits (Dickinson et al., 2008). IQ deficit may be an inherent, natural property of subjects at genetic risk instead of a confound and hence controlling it may have the effect of throwing the baby out with the bathwater (Miller and Chapman, 2001). Also, correlations between a dependent variable and a putative confound argue against controlling for that confound as it may obscure real group differences of the dependent variables (Miller and Chapman, 2001).

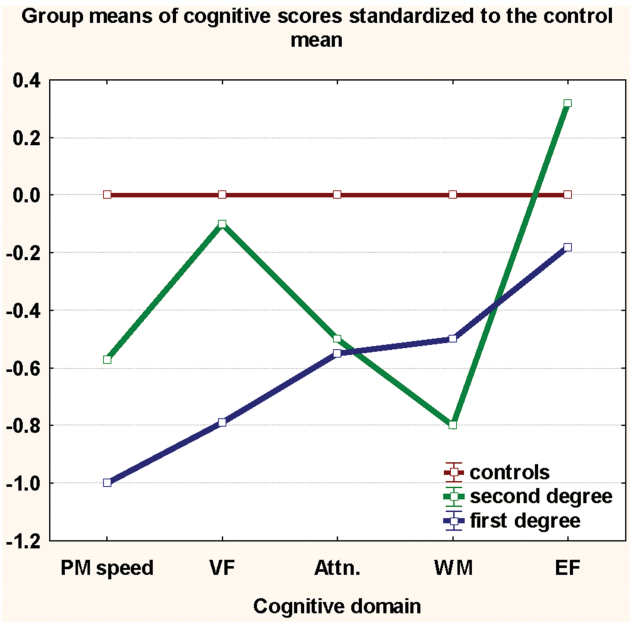

FIGURE 1 | Proximity of relatives to patients predicts poorer cognition. Cognitive scores for each group were *z*-transformed to the control mean. Group-means of the *z*-scores are plotted on the *y*-axis. PM, psychomotor; VF, verbal fluency; EF, executive function; Attn, attention; WM, working memory.

The spatial-working-memory deficits noted at the 12-s delay were absent for a 2-s delay. This supports previous evidence suggesting a task difficulty by group interaction when comparing SZ

patients with healthy controls where memory deficits in patients are evident only at high difficulty levels. Disproportionately high BOLD response in the DLPFC during low difficulty level WM tasks may interfere with the capacity of patients to increase DLPFC activity compared to baseline when presented with high difficulty tasks (Callicott et al., 1998, 2000; Tan et al., 2006). Longitudinal neurocognitive assessments are needed to explore further temporal decline in attention, verbal fluency, and psychomotor to detect a possible emergence of executive function and spatial WM deficits.

BRAIN STRUCTURAL CORRELATES OF NEUROCOGNITIVE DEFICITS

The Pittsburgh High-Risk Study also involved a structural brain-imaging component. Relatives were categorized into low cognitive scoring and high cognitive scoring groups based on verbal fluency, attention, psychomotor speed, and executive-function scores using K-means cluster analysis. This method is an iterative procedure, which clusters cases into two groups. The iterations seek to minimize within cluster variance and maximize variability between clusters in an ANOVA-like fashion. Brain regions involved in these cognitions and implicated in SZ were compared across low and high scoring clusters of relatives.

As seen in **Figure 2**, the low scoring subset of relatives ($n = 59$) had lower volumes in critical brain regions compared to the high scoring subset ($n = 35$), with the exception of the middle frontal gyrus. Relatives of patients show cognitive deficits that co-occur with alterations of regions mediating these compromised cognitions. This association may tentatively suggest structural alterations to underpin cognitive deficits seen in relatives. Brain regional abnormalities with their "downstream" attendant cognitive deficits may together be considered as "extended endophenotypes", a parsimonious conceptualization of SZ (Prasad and Keshavan, 2008).

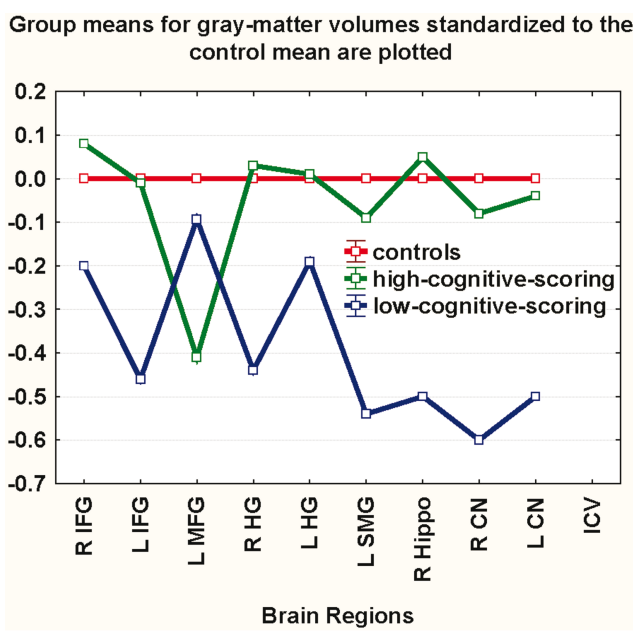

FIGURE 2 | The low scoring subset of relatives had volumetric deficits in critical brain regions compared to the high scoring subset. Regional gray-matter-volumes (right and left combined) for each group were z-transformed to the control mean. Group-means of the *z*-scores are plotted on the *y*-axis in the low-scoring and the high-scoring groups (see text for description of approach to this classification). HG, Heschl's gyrus; SMG, supramarginal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; Hippo, hippocampus; CN, caudate nucleus.

In summary, findings from the PREP study are consistent with previous reports of cognitive deficits in relatives of SZ patients and suggest that these deficits may be related to neuroanatomical deficits of corresponding brain regions. The existence of distinct subgroups of low and high cognitive scoring subjects within the sample of relatives is a critical finding from the PREP study. The clustering of structural alterations within the low-scoring subgroup tentatively suggests a neuroanatomically and cognitively compromised "hypervulnerable" subset within relatives with a familial diathesis for SZ. The risk of SZ and SZ spectrum disorders in genetically liable relatives of patients is 11–15% and about 40% (Diwadkar et al., 2006) respectively. This further suggests a heterogeneous risk-profile of the genetically vulnerable population for future psychotic illness and the occurrence of "hypervulnerable" subgroups (Diwadkar et al., 2006). The latent genetic heterogeneity in SZ explains the existence of these subgroups rather than a uniform vulnerability for SZ within genetically predisposed populations (Diwadkar et al., 2006; Eack et al., 2008).

CONCLUSIONS

In summary, cognitive deficits are a core feature of the premorbid vulnerability to SZ. Impairments are seen in several cognitive domains in unaffected relatives of patients including attention, WM, verbal memory, visual memory, executive function, speed of information processing, social cognition, and general intelligence. In general, the abnormalities appear more severe in first-degree relatives, and are associated with more prominent brain structural alterations. These observations are of clinical as well as pathophysiological significance.

An important question of clinical relevance is whether premorbid cognitive deficits can predict the emergence of later SZ in non-symptomatic at-risk subjects. As reviewed, the NYHRP and EHRS studies suggest that deficits in memory, attention, and social cognition in young relatives of SZ patients may predict later psychosis. Attention deficits in young relatives of SZ patients frequently have features of attention deficit disorder (Keshavan et al., 2003, 2008). This often leads to the clinical practice of treating such individuals with stimulant medications, which may have the undesirable effect of triggering psychosis in these vulnerable individuals. It is important to distinguish attentional impairments that are the precursors of a serious illness such as SZ and treat them with the disease appropriate interventions. Thus, children and adolescents newly presenting with attentional impairments should not, as often happens, be automatically diagnosed as having attention deficit disorders, but should be assessed to rule out early features of SZ (such as prodromal symptoms and schizotypy) or bipolar disorder (mood dysregulation). Inquiring for family histories of major psychiatric disorders is also important. Investigating premorbid neurocognitive deficits is also of importance for early intervention.

Further research is needed to evaluate the efficacy of cognitive remediation approaches, shown to benefit early phases of SZ (Eack et al., 2007), in at-risk individuals with cognitive deficits. Pharmacological interventions, including low dose atypical antipsychotics, have also been piloted in cognitively impaired relatives at risk for SZ (Tsuang et al., 1999).

Cognitive deficits, being core impairments in the premorbid phase of SZ, offer the best way to define the neurobiology of the vulnerability to this illness. As reviewed in this paper, cognitive deficits are robust, highly prevalent, stable, easily quantifiable, correlate with defined biological alterations in the illness, and are present in both those with the illness and those at risk. These features qualify cognitive impairments as endo- (or intermediate) phenotypes, which are beginning to pave the way to identification of the susceptibility gene(s) (Gur et al., 2007c).

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Does abnormal sleep impair memory consolidation in schizophrenia?

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Although disturbed sleep is a prominent feature of schizophrenia, its relation to the pathophysiology, signs, and symptoms of schizophrenia remains poorly understood. Sleep disturbances are well known to impair cognition in healthy individuals. Yet, in spite of its ubiquity in schizophrenia, abnormal sleep has generally been overlooked as a potential contributor to cognitive deficits. Amelioration of cognitive deficits is a current priority of the schizophrenia research community, but most efforts to define, characterize, and quantify cognitive deficits focus on cross-sectional measures. While this approach provides a valid snapshot of function, there is now overwhelming evidence that critical aspects of learning and memory consolidation happen offline, both over time and with sleep. Initial memory encoding is followed by a prolonged period of consolidation, integration, and reorganization, that continues over days or even years. Much of this *evolution* of memories is mediated by sleep. This article briefly reviews (i) what is known about abnormal sleep in schizophrenia, (ii) sleep-dependent memory consolidation in healthy individuals, (iii) recent findings of impaired sleep-dependent memory consolidation in schizophrenia, and (iv) implications of impaired sleep-dependent memory consolidation in schizophrenia. This literature suggests that abnormal sleep in schizophrenia disrupts attention and impairs sleep-dependent memory consolidation and task automation. We conclude that these sleep-dependent impairments may contribute substantially to generalized cognitive deficits in schizophrenia. Understanding this contribution may open new avenues to ameliorating cognitive dysfunction and thereby improve outcome in schizophrenia.

Keywords: sleep, schizophrenia, procedural learning, motor skill, memory consolidation, cognition, slow wave sleep, sleep spindles

INTRODUCTION

Sleep disorders are a prominent feature of many neuropsychiatric disorders. While often viewed as secondary, as these disorders may themselves diminish sleep quality (Benca, 1996), sleep deprivation can precipitate psychosis (Tyler, 1955; Wright, 1993, but see, Kahn-Greene et al., 2007), and there is growing evidence that sleep disorders can trigger or aggravate a range of psychiatric conditions (Wehr et al., 1987; Ford and Kamerow, 1989; Breslau et al., 1996; Turek, 2005; Huang et al., 2007; Germain et al., 2008; Sateia, 2009). Schizophrenia is no exception. Sleep disturbances in schizophrenia have been described since Kraepelin (1919) and are associated with poorer coping skills and diminished quality of life (Goldman et al., 1996; Hofstetter et al., 2005). Subjective sleep disturbance is a common complaint throughout the course of schizophrenia (Lieberman et al., 2005), including in the prodrome (Miller et al., 2003). It is anecdotally associated with the initial onset of psychosis, and may serve as a predictor of psychotic decompensation in remitted patients (Benson, 2006). The presence of sleep disturbance in antipsychotic-naïve and unmedicated patients indicates that abnormal sleep is not merely a side-effect of medications, but instead may be a core feature of schizophrenia (for meta-analysis see Chouinard et al., 2004). In fact, antipsychotic medications often normalize sleep in schizophrenia (Krystal et al., 2008), and medication withdrawal has been associated with a progressive deterioration of sleep quality (Nofzinger et al., 1993), which, in turn, is associated with psychotic relapse (Dencker et al., 1986) and increased severity of positive symptoms (Chemerinski et al., 2002). Although disturbed sleep is a prominent feature of schizophrenia, the nature of the abnormality and its relations to the pathophysiology, signs, and symptoms of schizophrenia remain poorly understood.

Sleep deprivation is well-known to impair cognition and to alter associated patterns of brain activation in healthy individuals (Horne, 1993; Van Dongen et al., 2003; Chee and Chuah, 2008). Yet, in spite of its ubiquity in schizophrenia, disturbed sleep has been largely overlooked as a potential contributor to cognitive deficits. While there is a general tendency to regard disturbed sleep as secondary to the illness, this neglect may be exacerbated by difficulty specifying the exact nature of the disturbance, and from a lack of awareness of the critical role of sleep in cognition. In addition, although the sleep disturbance in schizophrenia is often sufficiently severe as to warrant independent clinical attention, it is seldom the primary complaint, and its potential contribution to cognitive deficits is unlikely to be considered.

While cognitive deficits remain the strongest predictor of functional outcome in schizophrenia (Green et al., 2000), available antipsychotic medications are relatively ineffective in treating them (c.f., Sergi et al., 2007). Amelioration of cognitive deficits is a current priority of the schizophrenia research community, including government, academia, and industry, and is the focus of large-scale studies aimed at defining, characterizing, and quantifying these deficits for the purpose of evaluating the efficacy of interventions (e.g., Marder et al., 2004; Buchanan et al., 2007). A limitation of many of these efforts is that cognition is measured in cross-section. While this approach provides a valid snapshot of function, it does not capture critical aspects of learning and memory consolidation that happen offline, both over time and with sleep (e.g., Karni et al., 1998; Stickgold, 2005; Born et al., 2006; Brown and Robertson, 2007). Yet existing evidence, reviewed below, suggests that sleep-dependent processes are impaired in schizophrenia, and may contribute substantially to disability. We believe that understanding this contribution can open new and promising avenues for treatment.

There is now overwhelming evidence that initial memory encoding is followed by a prolonged period of consolidation, integration, and reorganization, that continues over days or even years (Schacter and Tulving, 1994). Much of this *evolution* of memories is mediated by sleep (Stickgold and Walker, 2007). It thus becomes important, when examining memory in schizophrenia, or in any neuropsychiatric disorder, to investigate deficits not only in initial encoding and recall, but also in time- and sleep-dependent memory processes. Even in cross-sectional measures of cognition, sleep should be considered as an important contributor to attention deficits that can blunt cognitive performance across domains, and are the most frequent and obvious casualty of poor sleep in healthy individuals. In this article, we will briefly review (i) what is known about abnormal sleep in schizophrenia, (ii) sleep-dependent memory consolidation in healthy individuals, (iii) recent findings of impaired sleep-dependent memory consolidation in schizophrenia, and (iv) implications of impaired sleep-dependent memory consolidation in schizophrenia. We conclude that abnormal sleep may contribute substantially to cognitive deficits in schizophrenia and should be a focus of study.

WHAT IS KNOWN ABOUT ABNORMAL SLEEP IN SCHIZOPHRENIA?

The most common subjective sleep complaints in schizophrenia are difficulty initiating and maintaining sleep (Chouinard et al., 2004; Benson, 2008; Cohrs, 2008). These complaints of insomnia have been verified by polysomnographic (PSG) recordings that show reduced sleep efficiency (total sleep time divided by time in bed), increased sleep onset latencies, and increased wake time after sleep onset (WASO), including in unmedicated and drug naïve patients (for meta-analyses see, Benca et al., 1992; Tandon et al., 1992; Lauer et al., 1997; Keshavan et al., 1998; Chouinard et al., 2004; Yang and Winkelman, 2006). Some studies also report alterations in circadian rhythms of hormone and activity patterns in schizophrenia (Rao et al., 1994; Martin et al., 2005) and increased rates of sleep disorders including sleep-related breathing disorders (e.g., obstructive sleep apnea), hypersomnolence, movement disorders (e.g., restless leg syndrome, periodic limb movement disorder), and parasomnias (for reviews see, Benson, 2006, 2008; Sateia, 2009).

PSG studies also report diverse abnormalities of sleep architecture (i.e., the amount and distribution of time spent in different sleep stages). Normal sleep in adult humans is divided into periods of rapid eye movement (REM) and non-rapid eye movement (NREM) sleep, with NREM sleep further divided into Stages 1–4 (**Figure 1**) (Rechtschaffen and Kales, 1968). Stages 3 and 4 are characterized by large (>75 μV) delta (0.5–2 Hz) waves in the EEG, and together constitute "slow wave sleep" (SWS). (This nomenclature has recently changed, and NREM Stages 3 and 4 are now combined into one stage (Iber et al., 2007), but we defer to the older nomenclature, as it is used in all the literature reviewed here.) A typical night of sleep is made up of 4–5 REM cycles, each beginning with NREM sleep and ending with REM sleep, and lasting approximately 90 min. While the cycle time is relatively constant across the night, most of the SWS occurs in the first half of the night, and most REM sleep occurs in the last half (**Figure 1**).

The most consistent electrophysiological sleep abnormality reported in schizophrenia is a decrease in the amount of SWS (Keshavan et al., 1990). Reductions have been reported in antipsychotic-naïve (Jus et al., 1968; Feinberg et al., 1969; Poulin et al., 2003), unmedicated (Keshavan et al., 1998; Yang and Winkelman, 2006), medicated (Goder et al., 2004), and remitted patients (Kupfer et al., 1970; Traub, 1972). Reduced SWS has also been observed in non-psychotic first-degree relatives of individuals with schizophrenia, suggesting that it is a trait associated with risk for schizophrenia (Keshavan et al., 2004). SWS reductions, however, are not consistently observed, even in antipsychotic-naïve patients (Tandon et al., 1992; Lauer et al., 1997) and have not survived meta-analysis (Chouinard et al., 2004). Caldwell and Domino (1967) reported that while 40% of patients showed almost a complete elimination of stage 4 SWS, the remaining 60% showed normal levels, suggesting that the reduction may characterize only a subset of patients. In addition, SWS changes are not specific to schizophrenia and are seen in major depression and other psychiatric disorders (Keshavan et al., 1990; Benca et al., 1992). Although abnormalities in REM sleep have also been reported, usually a decrease in REM latency (Tandon et al., 1992; Poulin et al., 2003) or an increase in REM density (Yang and Winkelman, 2006), meta-analyses have not revealed any systematic difference in REM sleep between patients and healthy or psychiatric controls (Benca et al., 1992; Chouinard et al., 2004). Both SWS and REM sleep abnormalities have been related to increased symptom severity, a literature that has been reviewed elsewhere (Benson, 2008).

Only a few studies have gone beyond sleep architecture to examine changes in the characteristics of the EEG power spectrum during sleep in schizophrenia. Slow wave activity and sleep spindles are

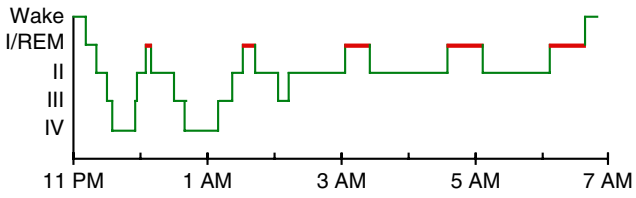

FIGURE 1 | A good night's sleep. The normal progression of sleep stages across a night of uninterrupted sleep. REM sleep is highlighted in red.

particularly relevant here since slow wave activity has been correlated with overnight improvement of motor procedural learning (Huber et al., 2004) and accumulating evidence suggests that sleep spindles mediate sleep-dependent consolidation of both procedural (Walker et al., 2002; Fogel and Smith, 2006; Nishida and Walker, 2007; Peters et al., 2008; Rasch et al., 2008; Tamaki et al., 2008) and declarative (Clemens et al., 2005, 2006; Schabus et al., 2008) memory. Sleep spindles, a defining characteristic of stage 2 sleep, are brief powerful bursts of synchronous 12–15 Hz neuronal firing in thalamo-cortical networks, which reach peak density late in the night (De Gennaro et al., 2000). Spindles induce massive influxes of calcium ions into cortical pyramidal cells, which are believed to trigger intracellular, calcium-dependent mechanisms required for synaptic plasticity (Sejnowski and Destexhe, 2000). In schizophrenia, there have been reports of reduced slow wave activity (Hiatt et al., 1985; Keshavan et al., 1998; Goder et al., 2006) during SWS. There have also been mixed reports of changes in sleep spindles, including increased spindle counts (Hiatt et al., 1985), and both unchanged (Poulin et al., 2003) and reduced (Ferrarelli et al., 2007) sleep spindle density.

All of the usual suspects contribute to difficulties in characterizing sleep in schizophrenia. These include differences in sample size, demographic features, chronicity, and the definition and measurement of sleep parameters. Discrepant findings may also relate to the underlying pathophysiological and phenotypic heterogeneity of schizophrenia. Finally, by affecting neurotransmitter systems that play an important role in sleep regulation, treatments for schizophrenia, including antipsychotic, anticholinergic, and anti-adrenergic medications, have diverse effects on sleep (Monti and Monti, 2004; and for reviews see, Benson, 2008; Krystal et al., 2008; Kantrowitz et al., 2009). Thus, factors such as medication status (naive vs. unmedicated vs. medicated), duration, and type all contribute to variability in sleep measurements. While, overall, antipsychotic medications tend to improve measures of sleep maintenance and to normalize sleep architecture (e.g., Maixner et al., 1998; Salin-Pascual et al., 1999), their effects on the sleep processes that mediate memory consolidation are largely unknown.

SLEEP-DEPENDENT MEMORY PROCESSING IN HEALTHY INDIVIDUALS

The last decade has produced a wealth of evidence for the role of sleep in the offline processing of recent memories, describing sleep-dependent events at the molecular, cellular, neural network, regional brain activation, and behavioral levels, in birds (Dave et al., 1998), rodents (Wilson and McNaughton, 1994), cats (Frank et al., 2001), and humans (Stickgold and Walker, 2007). This evidence suggests an evolutionarily conserved function for sleep in the stabilization, enhancement, integration, and reorganization of a wide range of memory types, functions that we will collectively refer to as 'consolidation.' Most relevant to this review are the findings from human studies.

PERCEPTUAL AND MOTOR PROCEDURAL LEARNING

Procedural or skill learning is a category of non-declarative memory for how to perform various perceptual and motor tasks. Many visual (Stickgold et al., 2000), auditory (Gaab et al., 2004), motor sequence (Walker et al., 2002), and motor adaptation (Huber et al., 2004) tasks show improvements in performance after a night of sleep, but not after an equivalent period of daytime wake. Because there is an absolute improvement after sleep, the benefit cannot be simply ascribed to a passive protection against interference, or even to an active stabilization of the memories, as has been suggested for other types of learning. Rather, we and others have proposed that sleep gives rise to performance improvements that are either caused by or accompanied by systems level reorganizations of the initial memories that facilitate task automation (Atienza et al., 2004; Kuriyama et al., 2004; Fischer et al., 2005; Chee and Chuah, 2008). In this context, automation refers to a shift from controlled, effortful performance to performance that proceeds more efficiently (i.e., is faster, less variable, less vulnerable to interference, and has fewer errors), with reduced demands on attention (Shiffrin and Schneider, 1977) and a corresponding shift in the brain networks that support performance (Jueptner and Weiller, 1998). While automation is known to develop with practice, there is now direct evidence that automation can also develop with sleep.

Overnight improvement on a procedural visual discrimination task correlates with SWS early in the night and REM sleep late in the night (Stickgold et al., 2000), with SWS appearing to stabilize the original memory and REM sleep subsequently enhancing it (Mednick et al., 2003). In contrast, improvement on a procedural motor sequence tasks correlates with Stage 2 NREM sleep late in the night (Walker et al., 2002). In this case, improvement is characterized by faster, more accurate and more uniform transitions within the sequence, suggesting automation of the motor program (Kuriyama et al., 2004; Fischer et al., 2005). These skill enhancements are accompanied by changes in task-related brain activation patterns, including reduced activation in regions such as prefrontal cortex that mediate the conscious monitoring of performance (Fischer et al., 2005; Walker et al., 2005). Evidence for sleep-dependent automation is also found in a study of auditory learning in which participants learned to detect a deviant tone in a complex tone sequence (Atienza et al., 2004), although sleep stage correlates of this automation were not determined. Sleep-dependent changes in the 'mismatch negativity' (MMN) and P3a event-related potentials generated by deviant tones suggest that sleep reduced the voluntary attentional effort required for successful stimulus discrimination.

VERBAL MEMORY

Verbal declarative memory also benefits from post-training sleep. Performance on a word-pairs cued recall task has consistently been found to be better after a night of sleep than after an equal period of daytime wake (Plihal and Born, 1997; Ellenbogen et al., 2009), and to show greater resistance to subsequent interference after sleep (Ellenbogen et al., 2006, 2009). At least some of these benefits correlate with times of night rich in SWS (Plihal and Born, 1997). Sleep also facilitates the selective retention of gist memory for word lists, resulting the next morning in a less accurate, but arguably more useful abstract memory, with enhanced gist and reduced detail (Payne et al., 2006). Interestingly, when gist is enhanced, improved memory recall correlates with decreases in SWS.

EMOTIONAL MEMORY

Declarative memory for emotional words and pictures is also enhanced by sleep. When individuals studied pictures with

either neutral or aversive objects placed on neutral backgrounds, subsequent recognition of the aversive objects, relative to their backgrounds, was enhanced after sleep compared to wake (Payne et al., 2008). In contrast, sleep offered no benefit for memory of neutral objects or their backgrounds. Thus, sleep seems to unbind complex scenes and selectively enhance memory for the emotional components.

COMPLEX COGNITIVE PROCEDURAL LEARNING

In addition to benefiting simple procedural and declarative memories, sleep can also produce striking benefits for more complex forms of learning, such as rule extraction and insight. Using the remote associates task (Mednick, 1962), Cai et al. (2009) reported that napping facilitates discovery of the target word that links three otherwise unrelated words together (*e.g.*, "heart", "sixteen", and "cookie" are linked by the word "sweet"), a benefit that correlates with the amount of REM sleep obtained after initial exposure to the word triads. Similarly, Wagner et al. (2004) have shown than sleep enhances insight into a more efficient method of solving a class of mathematical problems. In these and other instances (e.g., Ellenbogen et al., 2007), sleep facilitates the identification of associations and commonalities that are less easily discovered during wake. Interestingly, in some cases this identification leads to subsequent conscious awareness of the new information (e.g., Wagner et al., 2004; Cai et al., 2009), while in other cases improved performance develops without any conscious awareness (e.g., Djonlagic et al., 2005; Ellenbogen et al., 2007).

Looking across memory paradigms, it appear likely that individual sleep stages correlate not with types of memory, but rather with stages in the "consolidation" process. Overall, SWS appears to correlate with stabilization of memories, possibly through synaptic level processes that reinforce the memory in the form in which it was originally encoded. In contrast, REM sleep, and possibly Stage 2 NREM, appear to lead to systems level reorganization of memories, resulting in their enhancement, automation, and integration into larger associative networks.

IMPAIRED SLEEP-DEPENDENT MEMORY CONSOLIDATION IN SCHIZOPHRENIA

There are still relatively few investigations of the role of sleep in cognition in schizophrenia. One line of research suggests that impaired sleep exacerbates attention deficits. An early study showed that among unmedicated chronic schizophrenia patients ($n = 10$), those who made more errors of omission on a continuous performance test had significantly less SWS (Orzack et al., 1977). Similarly, Forest et al. (2007) reported that increased reaction time on tests of attention in antipsychotic-naïve patients with schizophrenia ($n = 8$) and healthy controls ($n = 8$) correlated with decreased sleep spindle density in both groups, and with Stage 4 SWS sleep duration only in schizophrenia. Finally, in a sample of chronic patients who had been withdrawn from their medications ($n = 15$), Yang and Winkelman (2006) clinical ratings of cognitive symptoms correlated with both decreased SWS and decreased REM density.

A second line of research suggests that impaired sleep in schizophrenia also leads to deficits in sleep-dependent memory consolidation and automation. In medicated schizophrenia patients ($n = 17$), reductions in SWS and sleep efficiency correlated with reduced recall of the Rey-Osterrieth Complex Figure, a test of visuospatial memory, following a night of sleep (Goder et al., 2004). In an exploratory study, Goder et al. (2006) found that slow wave activity in NREM sleep positively correlated with both better performance and overnight improvement on a range of neuropsychological measures in healthy controls. In contrast, medicated schizophrenia patients ($n = 16$), who showed reduced slow wave activity, showed relatively few significant correlations with slow wave activity, and these were evenly split between positive and negative correlations. In a recent study of chronic patients taking amisulpride ($n = 26$), Goder et al. (2008) reported that patients with more SWS had better recognition memory for words that were learned prior to sleep, as did those with a higher sleep spindle density.

Further evidence of impaired sleep-dependent memory consolidation in schizophrenia comes from two studies of procedural memory, one behavioral (Manoach et al., 2004) and one that included a night of PSG recording (Manoach et al., 2009), which used a finger tapping motor sequence task (MST, Karni et al., 1998) with chronic medicated patients with schizophrenia (Study 1: $n = 20$; Study 2: $n = 14$). In spite of intact practice-dependent learning during training, neither study found evidence of the subsequent sleep-dependent improvement in performance that was seen in healthy controls (**Figure 2**). The absence of significant overnight improvement in patients in the second study (Manoach et al., 2009) occurred in the context of no differences from controls in the amounts or distribution of time spent in specific sleep stages, or in any index of awakenings.

In healthy young adults, overnight improvement on the MST and other simple procedural motor skill tasks correlates with the amount of stage 2 NREM sleep in the last quarter of the night (S2q4, Smith and MacNeill, 1994; Walker et al., 2002; Fogel et al., 2007). MST improvement also correlates with the number and density of fast spindles (Rasch et al., 2008) as well as with an asymmetry of spindle density and power at central electrodes (right C4 > left C3), which may reflect selective changes in the right motor cortex related to learning since it was the left hand that performed the task (C4–C3, Nishida and Walker, 2007). In this context, it is striking that, compared to healthy controls, schizophrenia patients showed a significant 45% reduction in fast sigma frequency power, and 43% reduction in spindle density, at C4 during S2q4 sleep following MST training (Manoach et al., 2009).

Although patients with schizophrenia did not show significant overnight improvement as a group, there was considerable variability in the amount of improvement, which correlated with the amount of time spent in specific sleep stages (Manoach et al., 2009). As in young healthy individuals (Walker et al., 2002), time spent in S2q4 sleep predicted overnight improvement (**Figure 3A**), but so did SWS duration (**Figure 3B**), an effect not previously seen with the MST. When the product of SWS and S2q4 sleep was added to a regression model, their individual contributions were no longer significant, and only their product was, accounting for 77% of the variance in overnight improvement in schizophrenia (**Figure 3C**). This suggests that both SWS and S2q4 sleep are necessary for consolidation and is consistent with a two-stage model of procedural memory consolidation (Stickgold et al., 2000).

In a prior study of healthy individuals, overnight improvement on a visuoperceptual procedural learning task correlated with both

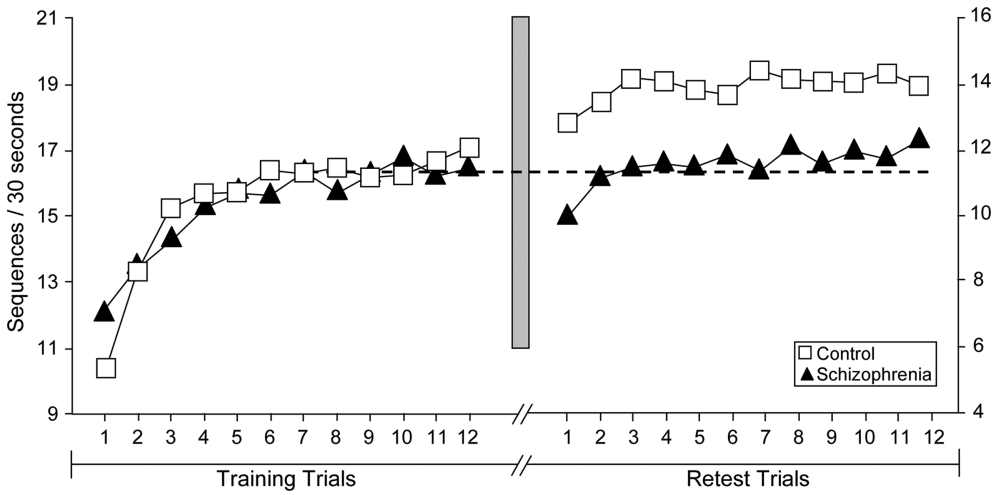

FIGURE 2 | Motor skill learning across training and test trials of the motor sequence task (MST) for healthy control participants (*n* = 14, open squares) and schizophrenia patients (*n* = 20, closed triangles) from Manoach et al. (2004). The data point for each trial represents the group average. The *y*-axes represent the number of correct sequences typed in each 30-s epoch. Note that the *y*-axes are scaled separately for controls (left) and patients (right) to better illustrate the qualitative similarity of learning curves on Day 1 and the failure of overnight improvement in the schizophrenia group only. The dashed line is positioned at the mean value of the last three training trials for both the control and patient groups. The shaded bar represents the passage of 24 h, including a night of sleep. Patients and controls did not differ in the amount of learning during training, but only controls showed significant overnight improvement.

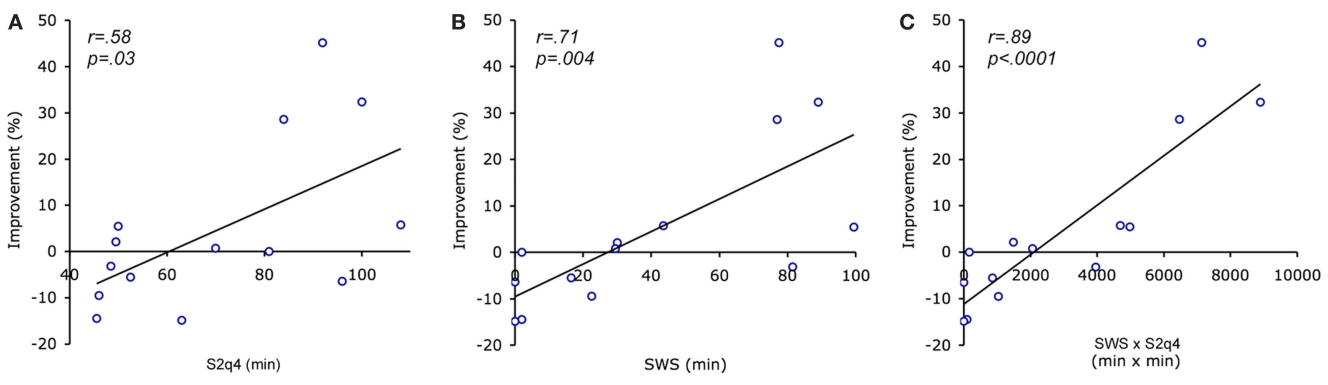

FIGURE 3 | Correlation of overnight improvement with minutes spent in slow wave sleep (SWS) and stage 2 sleep in the last quartile of the night (S2q4) in schizophrenia patients. (A) Correlation with S2q4 sleep; **(B)** Correlation with SWS; **(C)** Correlation with the product of SWS and S2q4 sleep (SWS x S2q4).

SWS early in the night and REM sleep in the last quarter, but even more strongly with their product (Stickgold et al., 2000). A subsequent study of naps showed that while naps containing SWS prevented deterioration in visuoperceptual performance over the day, naps with both SWS and REM sleep led to same-day improvement (Mednick et al., 2002). These findings suggest that SWS, which is predominant early in the night, stabilizes visuoperceptual procedural memory, while REM sleep later in the night enhances it. A similar model fits our motor procedural memory consolidation findings in schizophrenia (Manoach et al., 2009). While both SWS and S2q4 sleep correlated with improvement measured at the start of the test session, when this initial improvement was broken into its component parts, a striking double dissociation was seen. SWS appeared to prevent the delayed expression of improvement, which characterizes MST performance in healthy middle-aged (Manoach et al., 2004) and elderly participants (McKinley, 2008), while S2q4 sleep appeared to facilitate the sleep-dependent enhancement seen after this delay.

These findings provide direct evidence of a deficit in sleep-dependent memory consolidation in medicated patients with chronic schizophrenia. That this deficit occurred in the context of normal sleep architecture suggests that it is not the amount or distribution of time spent in different sleep stages that is culpable, but rather specific memory consolidation processes that are normally activated during sleep (Manoach et al., 2004), particularly processes occurring during SWS and S2q4 sleep. An important caveat is that the samples in these two studies were too small and the medications, which were clinically determined, were too diverse to adequately evaluate medication effects. Although antipsychotic dose, as measured by chlorpromazine equivalent, was not correlated with any

measure of overnight improvement, a study of medication-naïve patients would be required to determine the extent to which deficits in sleep-dependent memory consolidation reflect medication side-effects versus a disease process.

IMPLICATIONS OF IMPAIRED SLEEP-DEPENDENT MEMORY CONSOLIDATION IN SCHIZOPHRENIA

Sleep facilitates a wide range of processes that mediate the evolution of memories over time. These sleep-dependent processes aid in the stabilization, strengthening, integration, and reorganization of memories to increase their durability, flexibility, and automation. If *all* sleep-dependent memory processing were lacking, we suspect that this would impair not only the fine-tuning of complex skills and memories, but would also lead to profound difficulties in carrying out the basic activities of daily life.

There are still very few studies of the role of sleep in the cognitive deficits of schizophrenia. These early studies have small samples and many simply correlate sleep measurements with cross-sectional measures of neuropsychological performance, suggesting that sleep affects cognitive performance, primarily attention, in schizophrenia, as it does in healthy individuals. The few studies that evaluated the role of sleep in memory consolidation by comparing performance prior to and following a night of sleep have documented reduced overnight improvement in patients as a group, even in the context of comparable sleep architecture. Unfortunately, these studies have only included medicated patients. But regardless of the underlying mechanisms and whether they reflect treatment or disease process, findings of impaired sleep-dependent memory consolidation have important implications for understanding and treating cognitive dysfunction in schizophrenia.

We propose that the observed failures of sleep-dependent memory consolidation represent a breakdown, not in the overall structure of sleep, but rather in specific memory consolidation processes that are normally activated during sleep. These sleep-dependent memory processes normally lead to task automation, resulting in performance that is faster, less variable, and less dependent on voluntary attention (Atienza et al., 2004; Kuriyama et al., 2004) and to more efficient patterns of brain activation, particularly in the prefrontal cortex (Fischer et al., 2005; Walker et al., 2005; Chee and Chuah, 2008). These recent findings of reduced sleep-dependent memory consolidation support the hypothesis of deficient automation in schizophrenia (Granholm et al., 1991; Manoach et al., 2000; Manoach, 2003) and extend this hypothesis to sleep-dependent processes. A fundamental breakdown in sleep-dependent automation in schizophrenia would make it necessary to allocate limited-capacity attentional resources to task elements that, in healthy individuals, have been automated as a function of sleep. This would leave fewer resources available for higher-order task demands that require cognitive control. It is this interaction between automatic and controlled processes that normally allows a limited capacity brain to carry out complex cognitive tasks. An impairment in sleep dependent automation could contribute substantially to the generalized cognitive deficits that are a hallmark of schizophrenia (Chapman and Chapman, 1978; Dickinson and Harvey, 2009).

CONCLUDING REMARKS

Sleep disturbances are common in schizophrenia. From a purely clinical perspective, they should be vigorously treated since in schizophrenia, like in other psychiatric disorders (Fava et al., 2006; Manber et al., 2008), treating sleep may also improve symptoms. The existing literature, reviewed here, suggests that treating sleep may also improve cognition in schizophrenia. But to identify targets for treatment, it is important to understand the mechanisms underlying normal sleep-dependent memory consolidation, how these are altered in schizophrenia, and how they are affected by medications. Understanding the contribution of sleep to cognitive deficits, and clarifying the role of medications in mediating these effects, may open new avenues to ameliorating cognitive dysfunction and thereby improve outcome in schizophrenia.

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Cannabis use and cognition in schizophrenia

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People with schizophrenia frequently report cannabis use, and cannabis may be a risk factor for schizophrenia, mediated through effects on brain function and biochemistry. Thus, it is conceivable that cannabis may also influence cognitive functioning in this patient group. We report data from our own laboratory on the use of cannabis by schizophrenia patients, and review the existing literature on the effects of cannabis on cognition in schizophrenia and related psychosis. Of the 23 studies that were found, 14 reported that the cannabis users had better cognitive performance than the schizophrenia non-users. Eight studies reported no or minimal differences in cognitive performance in the two groups, but only one study reported better cognitive performance in the schizophrenia non-user group. Our own results confirm the overall impression from the literature review of better cognitive performance in the cannabis user group. These paradoxical findings may have several explanations, which are discussed. We suggest that cannabis causes a transient cognitive breakdown enabling the development of psychosis, imitating the typical cognitive vulnerability seen in schizophrenia. This is further supported by an earlier age of onset and fewer neurological soft signs in the cannabis-related schizophrenia group, suggesting an alternative pathway to psychosis.

Keywords: schizophrenia, psychosis, cannabis, neurocognition, substance abuse, neuropsychological functioning, illegal drugs

INTRODUCTION

A history of cannabis use is more common in schizophrenia than in the normal population (Regier et al., 1990; Arseneault et al., 2004b; Barnes et al., 2006). Life-time cannabis use has been reported to be as high as 64.4% in patients with schizophrenia (Barnes et al., 2006), and Løberg et al. (2003) found that 45% of schizophrenia patients participating in research studies had a history of previous cannabis use. Since cannabis may be a risk factor for schizophrenia, mediated through changes in brain functioning and biochemistry, cannabis may also have an effect on cognitive functioning in this patients group. In a preliminary study in our laboratory we were struck by apparent paradoxical positive effects of cannabis on cognition in patients with schizophrenia (Løberg et al., 2003, 2008). These preliminary findings prompted a review of the existing literature on the relationship between cannabis use and cognitive functioning in schizophrenia. For this purpose, we found 23 studies (see **Table 1**) that have looked at the relationship between cannabis use and cognitive impairments in schizophrenia. The results from the review are discussed and possible explanations suggested.

CANNABIS USE – A RISK FACTOR FOR SCHIZOPHRENIA?

Longitudinal studies have reported an increased risk for schizophrenia and other psychoses after cannabis use. In two large-scale Swedish studies, the same cohort of about 50 000 military conscripts were for followed longitudinally over 15 and 26 years. Dose-dependent relationships were found between cannabis use at 18 years of age and a later diagnosis of schizophrenia (Andreasson et al., 1987; Zammit et al., 2002). Cannabis have also been shown to increase the rate of conversion to psychosis in individuals at risk for psychosis (Kristensen and Cadenhead, 2007). Furthermore, several large-scale longitudinal studies have reported a relationship between cannabis use in adolescence and later symptoms of psychosis in the normal population (Tien and Anthony, 1990; Arseneault et al., 2002; van Os et al., 2002; Fergusson et al., 2003; Stefanis et al., 2004; Ferdinand et al., 2005; Henquet et al., 2005a). In one study, cannabis use at age 18 and 21 led to 3.7 and 2.3 higher rates of psychotic symptoms, respectively (Fergusson et al., 2003). The relationship between cannabis and schizophrenia seems fairly specific to schizophrenia, as compared to other mental disorders (Chambers et al., 2001; Degenhardt et al., 2007; Di Forti et al., 2007; Moore et al., 2007), and cannot be explained by potentially confounding factors, like premorbid disorders, drug use, intoxication, personality traits, sosiodemographic markers and intellectual ability (Smit et al., 2004; Moore et al., 2007). Accordingly, five recent reviews concluded with an increased risk for schizophrenia and psychosis in individuals who have used cannabis (Arseneault et al., 2004b; Macleod et al., 2004; Smit et al., 2004; Henquet et al., 2005b; Semple et al., 2005; Moore et al., 2007).

An alternative explanation is what can be called reversed causality, namely that schizophrenia patients use cannabis as a form of self-medication, although existing data does not seem to support this hypothesis (Chambers et al., 2001). An important argument against reversed causality is an "order-effect"; i.e. cannabis use seems to occur before the outbreak of psychosis, and not the other way around (Linszen et al., 1994; Degenhardt et al., 2007; Corcoran et al., 2008). Furthermore, in contrast to a self-medication hypothesis, the psychoactive substance in cannabis, delta-(9)-tetrahydrocannabinol (THC), increases, and not decreases, anxiety (Fusar-Poli et al., 2009; Morrison et al., 2009). Several studies have also shown that THC increases symptoms

Table 1 | Overview of 23 studies on the effects of cannabis/drug use in schizophrenia and related psychoses on cognition by n, drug type, diagnoses, type of drug use, and results.

n: drug group/no-drug group	Multiple drugs or cannabis	Diagnostic characteristics	Current or former drug use, SUD if diagnosed	Cognitive results: drug group versus no-drug group	Reference
33/33 (13 in no-drug group had former drug use)	Multiple drugs	Schizophrenia (outpatients)	Current (SUD)	No difference	Addington and Addington (1997)
110/42	Multiple drugs	Schizophrenia + schizophreniform	Both	No difference	Barnes et al. (2006)
22 (moderate); 16 (severe)/25	Multiple drugs	Schizophrenia	Former	No difference	Cleghorn et al. (1991)
18/59	Cannabis	Non-affective psychoses + mood disorder	Current (SUD)	Minimal difference	Liraud and Verdoux (2002)
128/138	Multiple drugs	First episode psychoses	Current (SUD)	No difference	Pencer and Addington (2003)
14/13	Cannabis	Schizophrenia + schizoaffective	Current (SUD)	No difference	Sevy et al. (2007)
21/23	Multiple drugs	Schizophrenia + schizoaffective (recent onset)	Current	Minimal difference	Wobrock et al. (2007)
27/23	Multiple drugs	Schizophrenia (paranoid type)	Current (SUD)	Minimal difference	Thoma and Daum (2008)
15 (current); 26 (former)/15	Multiple drugs	Psychiatric outpatients	Both (SUD)	Better in both drug groups	Carey et al. (2003)
44/15	Cannabis	Schizophrenia + schizoaffective	Both	Better in drug group	Coulston et al. (2007a)
46/43	Multiple drugs	Schizophrenia (inpatients)	Current (SUD)	Better in drug group	Herman (2004)
19/20	Cannabis	Schizophrenia	Former	Better in drug group	Jockers-Scherubl et al. (2007)
16/14	Multiple drugs	Schizophrenia (men only)	Current (SUD)	Better in drug group	Joyal et al. (2003)
12/16	Cannabis	schizophrenia + schizoaffective (adolescent)	Former	Better in drug group	Kumra et al. (2005)
13/13	Cannabis	Acute psychoses	Current	More improved in drug group	Løberg et al. (2008)
13/16	Cannabis	Schizophrenia	Former	Better in drug group	Løberg et al. (2003)
57 (mild); 35 (severe)/91	Multiple drugs	First episode psychoses	Current (severe = SUD)	Better in both drug groups	McCleery et al. (2006)
44/32	Multiple drugs	Schizophrenia + schizoaffective	Current (SUD)	Better in drug group	Potvin et al. (2005)
35/34	Cannabis	Schizophrenia + schizoaffective	Former (SUD)	Better in drug group	Schnell et al. (2009)
27/91	Multiple drugs	Schizophrenia + schizoaffective	Both (SUD)	Better in drug group	Sevy et al. (2001)
26/37	Cannabis	First episode psychoses	Both	Better in drug group	Stirling et al. (2005)
27/23	Multiple drugs	Schizophrenia	Current (SUD)	Better in drug group	Thoma et al. (2007)
61/71	Cannabis	Non-affective psychoses	Former	Better in no-drug group	Mata et al. (2008)

of psychosis and cognitive impairments (D'Souza et al., 2005; Morrison et al., 2009), with a possible increased sensitivity in schizophrenia to the adverse effects of THC (D'Souza et al., 2004). Moreover, cannabis has been shown to have clinical significance. Cannabis use in schizophrenia can lead to worsened illness prognoses; worsened clinical outcome, longer psychotic episodes, more relapse and re-hospitalizations, poorer social functioning, more frequent relapses, poorer compliance, and increased treatment needs (Linszen et al., 1994; Caspari, 1999; Grech et al., 2005). Thus, taken together, the available data seem to point to cannabis use as increasing psychotic symptoms, and increasing the vulnerability for a psychotic outbreak. For example, Moore and colleagues have argued that we now know enough to warn young people about the risk for psychosis after cannabis use (Moore et al., 2007).

However, most individuals do not develop schizophrenia after cannabis use, suggesting that a heightened risk for a development of psychosis must be related to other vulnerability factors. Verdoux (2004) found that subjects with established vulnerability for psychoses showed a stronger risk of follow-up psychosis after cannabis use than individuals without such vulnerability. The relationship between cannabis use and psychosis may also be genetically mediated. In a longitudinal study of 803 individuals, an interaction between the Val allele of the Catechol-*O*-methyltransferase (COMT) gene and adolescent cannabis use significantly increased the likelihood of exhibiting psychotic symptoms and the development of schizophreniform disorders (Caspi et al., 2005). In accordance with this, an interaction between the COMT Val allele and sensitivity for psychosis and cognitive effects of the psychoactive substance in cannabis has been found in individuals with psychosis and their relatives (Henquet et al., 2006, 2009).

CANNABIS AND BRAIN FUNCTION

The relationship between cannabis and schizophrenia may be attributed to effects of cannabis on brain functioning and biochemistry. The endogenous cannabinoid system may directly or

indirectly be involved in the development of the effects of cannabis on symptoms of psychosis and cognition (Solowij and Michie, 2007). THC affects cannabinoid receptors, which are distributed with high density in the cerebral cortex, including brain regions implicated in schizophrenia (D'Souza et al., 2005). The endogenous cannabinoid system interacts with the dopaminergic system of the brain, and THC influence dopamine synthesis and uptake (D'Souza et al., 2005). Abnormalities of the endogenous cannabinoid system in schizophrenia, not caused by cannabis use, have also been reported. Increased levels of endogenous cannabinoids have been found in the frontal cortex (Dean et al., 2001), in addition to elevated levels of endogenous cannabinoids in the cerebral spinal fluids (Leweke et al., 1999).

A stronger relationship between adolescent cannabis use and psychosis or schizophrenia, as compared to adult use, has been reported in several studies (Caspi et al., 2005; Konings et al., 2008). Even though some of these findings can be explained by an increased cumulative exposure to cannabis with earlier onset of cannabis use, it may also suggest that a developing brain is more vulnerable to the effects of cannabis than a matured brain.

However although there seems to be ample evidence for the influence of cannabis on the development and outbreak of psychosis or schizophrenia (Moore et al., 2007), possibly mediated by adverse effects on brain functioning acting on the dopaminergic system (D'Souza et al., 2005), much less is known regarding the effects of cannabis use on *cognitive functioning* in schizophrenia. If cannabis influences schizophrenia neurodevelopment and brain functioning, it could be expected that cannabis use may impact on cognitive functioning in this patients group. The aim of the present review was therefore to examine the relationship between cannabis use and cognitive functioning in schizophrenia.

COGNITION IN PATIENTS WHO USE CANNABIS – A PARADOX

Cognitive impairment is now universally recognized as a core feature of schizophrenia, and clinically relevant cognitive impairments are observed in a majority of patients with schizophrenia (Green, 1996; Palmer et al., 1997, 2009). Cognitive impairment is often observed before the development of psychosis and in close relatives, and cognitive symptoms may also reside after clinical symptoms have been reduced or are no longer seen (Neuchterlein et al., 1994; Weinberger, 1995; Heaton et al., 2001; Gschwandtner et al., 2003), Thus, it is clear that eventual effects of cannabis use on cognitive functioning in schizophrenia would be of both theoretical value for the understanding of the disorder, and of clinical relevance for the diagnosis and treatment of the disorder. Intuitively, a worsened outcome on cognitive functioning would be expected after cannabis use, since cannabis has negative effects on psychosis in general, and from findings that cannabis use impairs illness prognosis (Linszen et al., 1994; Caspari, 1999; Grech et al., 2005), in addition to the adverse effects of cannabis on brain functioning (D'Souza et al., 2004).

For this purpose we reanalyzed previously collected data in our laboratory on cognitive performance in schizophrenia patients, including cannabis use as an explanatory variable (data from Løberg et al., 2003, 2008). Information on the history of cannabis use was based on the patients' clinical records and therapist questionnaires, and was further validated through SCID-interviews. Surprisingly, we found that patients with schizophrenia who had a history of

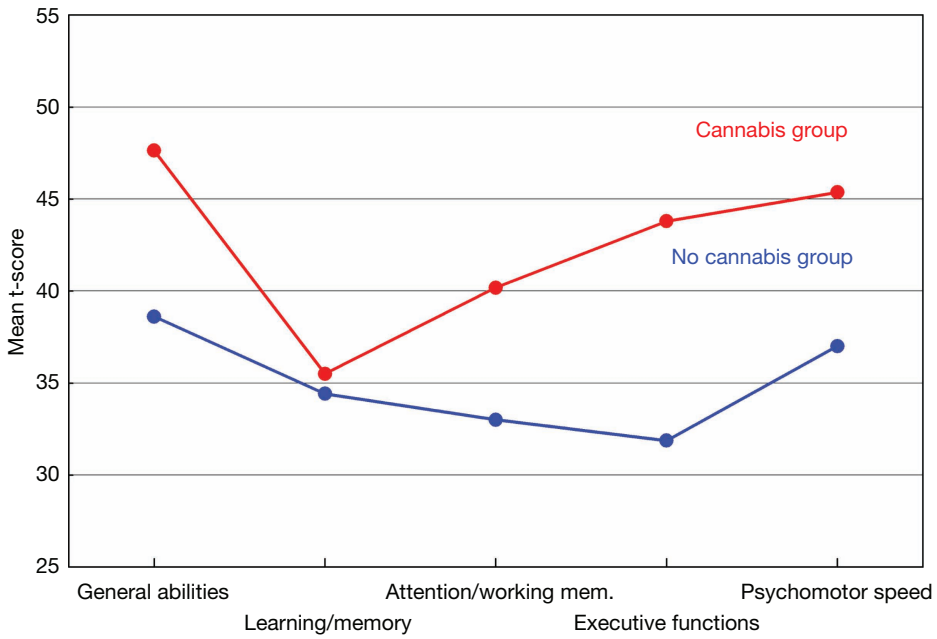

FIGURE 1 | Mean T-scores for the cannabis and no-cannabis group for the five cognitive functions. General abilities = general verbal and visuospatial abilities = WAIS (Information, Vocabulary, Block Design), Verbal Fluency (FAS), Rey-Osterrieth Complex Figure test, Wisconsin Card Sorting Test (WCST). Learning/memory = California Verbal Learning Test (CVLT) II, Rey-Osterrieth Complex Figure Test. Attention/working mem. = attention/working memory = Digit Vigilance Test, Calcap Continuous Performance Test (CPT), Trail Making Test B. Execute functions = Wisconsin Card Sorting Test (WCST), Stroop Test. Psychomotor speed = Trail Making Test A, Grooved Pegboard Test, Fingertapping Test.

cannabis use scored significantly above their fellow counterparts without a history of cannabis use (see **Figure 1**). This was found for almost all cognitive functions investigated, such as general intellectual ability, executive functions, attention, working memory and psychomotor speed. These results did not change when other illegal drugs where controlled for, and there were no differences in the two groups with regard to clinical variables (Løberg et al., 2003).

In a second, prospective, study of patients with acute psychosis we assessed cognitive function at admission to a psychiatric emergency ward, after 6 weeks, and after 3 months. Information on the history of cannabis use was based on patient's clinical records and the Clinician Drug Use Scale (Drake et al., 1990), and was further validated through urine samples. The patients with both cannabis use and psychosis showed a significantly larger improvement in their cognitive performance in the three months after admission, as compared to the psychotic patients with no cannabis use. Both groups showed cognitive impairments at admission, but these were more prevalent in the non-cannabis psychosis group (see **Figure 2**; Løberg et al., 2008).

COGNITION IN PATIENTS WHO USE CANNABIS – A LITERATURE REVIEW

The paradoxical results reported by Løberg et al. (2003, 2008) seem to be consistent with several other studies on the relationship between cognition, cannabis and/or illegal drugs and schizophrenia (Joyal et al., 2003; Jockers-Scherubl et al., 2007). We performed a PubMed search on all combinations of the following search words: *cannabis, substance, schizophr*, psychos*, cognit* and neuropsych**, and searched the reference lists for all included papers of other studies covering this topic. This resulted in 23 studies comparing schizophrenia and related psychoses with and without cannabis use (alone or in combination with other substances) on cognitive performance (see **Table 1** for further details).

Fourteen of the studies listed in **Table 1** reported that the cannabis groups showed better cognitive performance than the no-cannabis groups (Sevy et al., 2001; Carey et al., 2003; Joyal et al., 2003; Løberg et al., 2003, 2008; Herman, 2004; Kumra et al., 2005; Potvin et al., 2005; Stirling et al., 2005; McCleery et al., 2006; Coulston et al., 2007a; Jockers-Scherubl et al., 2007; Thoma et al., 2007; Schnell et al., 2009). Eight of the studies in **Table 1** reported no or minimal differences in cognitive performance in the two groups (Cleghorn et al., 1991; Addington and Addington, 1997; Liraud and Verdoux, 2002; Pencer and Addington, 2003; Barnes et al., 2006; Sevy et al., 2007; Wobrock et al., 2007; Thoma and Daum, 2008), and one study reported better cognitive performance in the no-cannabis compared to the drug group (Mata et al., 2008).

Most of the studies in **Table 1** have small "*n*", and may therefore be influenced by Type-II statistical errors (false negatives), underestimating group differences due to lack of power. For instance, Thoma and Daum (2008) suggested that this may have been a problem in their 2008 study, influencing their conclusion of no differences between the groups. Furthermore, some of the studies included diverse drug use in addition to cannabis use, for instance alcohol and opiates in clusters of stimulating and/or hallucinatory illegal drugs. These drugs may have different, and sometimes opposite effects on brain functioning and neurochemistry, and consequently on cognition. In the overview in **Table 1**, all studies included cannabis; as a high frequent drug together with other drugs used, or as the only drug used. Thus, no study was included that did not include cannabis. Previous drug

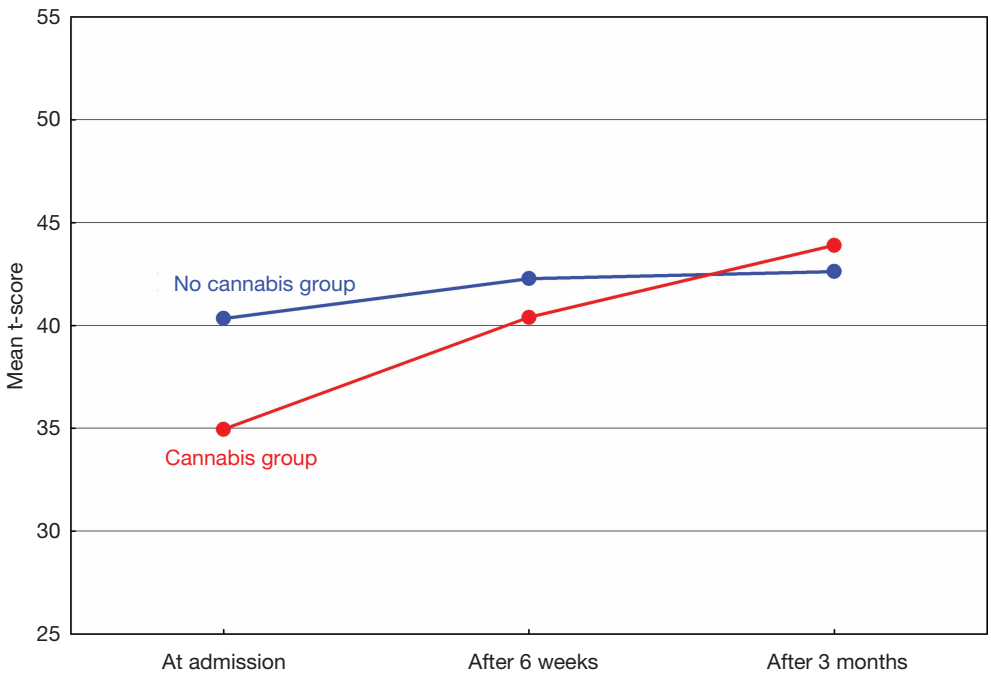

FIGURE 2 | Mean neuropsychological T-scores for the cannabis and no-cannabis group at admission, after 6 weeks and 3 months.

use versus current drug use is included in **Table 1** as a separate factor since this may have influenced the results. Current drug use may influence cognition by means of persisting intoxication effects or more acute effects on brain functioning, thus creating a "false" cognitive impairment not otherwise present. Furthermore, the use of diagnostic criteria is noted, yielding a SUD, since this usually means that the patients meet criteria for abuse or addictive behavior, and that the drug use has negative consequences for everyday living. This may bias the drug groups to consist of quite heavy users due to the exclusion of patients without a SUD diagnosis who nevertheless may have a frequent drug problem. An example of this is the study by Addington and Addington (1997) where it was reported that the no-drug group actually included 13 patients with previous drug use. Another problem when comparing the studies in **Table 1** is the different diagnostic groups included in the studies, possibly with different levels of cognitive vulnerability.

Coulston et al. (2007b) did not find consistent neuropsychological patterns of cannabis use on cognition when examining seven studies (one of these studies reported intoxications effects, though), and attributed this to methodological variability between and methodological limitations within the studies. Methodological and clinical heterogeneity is also a problem in studies comparing differences in brain structure and function between drug and no-drug groups by means of brain-imaging methods, and inconsistent results have been reported (Quickfall and Crockford, 2006; Rais et al., 2008; Wobrock et al., 2009).

CONCLUSION LITERATURE REVIEW

Table 1 show that a majority of the studies report better cognitive functioning in the cannabis-related schizophrenia and psychosis groups compared to non-drug groups. This conclusion is supported even when confounding factors, like age, years of education, premorbid IQ, medical history, substance use, and psychiatric symptoms (Coulston et al., 2007a) are controlled for. Likewise, Potvin et al. (2008) argued that most studies have shown superior neuropsychological functioning in cannabis use and schizophrenia combined, then in schizophrenia patients alone (Potvin et al., 2008).

EXPLANATIONS FOR THE PARADOXICAL EFFECT

The seemingly paradoxical cognitive findings in cannabis-related schizophrenia could have several explanations. One explanation is that the group differences in cognition are attributed to superior social skills in the cannabis schizophrenia groups, making them "skillful" enough to get hold of illegal drugs. Superior social skills are however not consistent with the finding of poorer prognosis in this group. Few studies have, however, examined this directly, and the issue therefore remains unresolved. Two Norwegian studies reported poorer premorbid functioning in psychosis patients who also abused illegal drugs (Ringen et al., 2008), and better premorbid social functioning and poorer premorbid academic functioning in this group (Larsen et al., 2006), respectively. It has also been suggested that the group differences could be caused by cannabis having a protective or positive influence on brain functioning (Coulston et al., 2007a). Based on the effects of cannabis on brain function and prognosis of the psychosis, this is not supported by the existing data.

A second explanation could be that cannabis imitates the typical cognitive vulnerability seen in schizophrenia. The major psychoactive component in cannabis, THC, creates transient negative effects on cognitive functioning and psychotic symptoms (D'Souza et al., 2005; Semple et al., 2005; Morrison et al., 2009). Cannabis use of sufficient magnitude, or in individuals particularly vulnerable to the effects of cannabis, may lead to compromised brain functioning, causing a breakdown of reality testing. In addition, adolescent cannabis use seems to cause an especially strong risk for later psychosis (Caspi et al., 2005; Konings et al., 2008), consistent with a sensitive adolescent brain in the middle of important neurodevelopmental processes. Thus, cannabis would induce more transient cognitive changes that mimic the typical cognitive vulnerability. These changes can cause psychosis for some individuals, but will normally not cause the characteristic persistent cognitive impairments seen in schizophrenia. Consistent with this, fewer neurological soft signs have been shown in schizophrenia patients who also use cannabis (Bersani et al., 2002; Ruiz-Veguilla et al., 2009). Stirling et al. (2005) also reported fewer neurological soft signs, and better cognitive functioning, in the drug group after 10–12 years, and suggested that the drug group followed a different path to schizophrenia with less negative events of early brain development.

Further support for the imitation of cognitive vulnerability hypothesis is findings regarding age of onset of the disorder. The development of schizophrenia is usually seen in late adolescence/early adulthood. This is in line with a neurodevelopmental model (Weinberger, 1995), since the age of onset coincides with the late maturation of the prefrontal cortex through pruning of exuberant synapses and myelination of axons (Woo and Crowell, 2005). Studies have reported earlier age of onset in schizophrenia patients who have used cannabis (Stirling et al., 2005; Barnes et al., 2006). Consistent with this, data from our own laboratory showed four years earlier debut of schizophrenia in cannabis users (Løberg et al., 2003). Again, this suggests a different pathway to schizophrenia, and is consistent with a hypothesis stating that cannabis is an environmental factor imitating the effect of the typical cognitive vulnerability (Solowij and Michie, 2007).

CONCLUDING REMARKS

Cannabis seems to be a risk factor for the development of schizophrenia, mimicking the typical cognitive vulnerability. As an environmental factor, cannabis use has the potential for being influenced by interventions, thus indirectly having an effect on the development of schizophrenia. Accordingly, clinical implications (Moore et al., 2007) and public health implications (Arseneault et al., 2004a) have been suggested. A promising clinical intervention would be to monitor cannabis use in patients known to be vulnerable for psychosis, and help them to stay away from cannabis. Cannabis does not appear to create additive cognitive impairments, however, and cannabis-using patients may actually have better cognitive functioning. This could suggest that cannabis-related schizophrenia represents a different subtype, although few consistent clinical differences in regard to symptom profiles have been found (Boydell et al., 2007). This necessitates a better understanding of the paradox of better cognitive functioning, similar clinical profiles, and worse prognosis in this group, through for instance

longitudinal studies on the effect of previous and ongoing cannabis use on the fluctuations of cognitive and clinical functioning in schizophrenia.

Possibly cannabis mimics the typical cognitive vulnerability seen in schizophrenia. Solowij and Michie (2007) suggested that cannabis leads to similar cognitive impairment as what is typically seen in schizophrenia, but of a lower magnitude. Several studies have shown cognitive impairment during THC-intoxication (D'Souza et al., 2005; Morrison et al., 2009). The preliminary data from our own laboratory suggest more transient cognitive impairments in the cannabis group (Løberg et al., 2008). Perhaps cannabis causes a transient cognitive breakdown enabling the development of psychosis, in spite of the absence of proper cognitive vulnerability. Thus, the effects of cannabis on cognition and brain functioning model the cognitive vulnerability in schizophrenia, and understanding this cognitive breakdown may provide a unique window to understanding schizophrenia neurodevelopment.

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Functional brain networks in schizophrenia: a review

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Functional magnetic resonance imaging (fMRI) has become a major technique for studying cognitive function and its disruption in mental illness, including schizophrenia. The major proportion of imaging studies focused primarily upon identifying regions which hemodynamic response amplitudes covary with particular stimuli and differentiate between patient and control groups. In addition to such amplitude based comparisons, one can estimate temporal correlations and compute maps of functional connectivity between regions which include the variance associated with event-related responses as well as intrinsic fluctuations of hemodynamic activity. Functional connectivity maps can be computed by correlating all voxels with a seed region when a spatial prior is available. An alternative are multivariate decompositions such as independent component analysis (ICA) which extract multiple components, each of which is a spatially distinct map of voxels with a common time course. Recent work has shown that these networks are pervasive in relaxed resting and during task performance and hence provide robust measures of intact and disturbed brain activity. This in turn bears the prospect of yielding biomarkers for schizophrenia, which can be described both in terms of disrupted local processing as well as altered global connectivity between large-scale networks. In this review we will summarize functional connectivity measures with a focus upon work with ICA and discuss the meaning of intrinsic fluctuations. In addition, examples of how brain networks have been used for classification of disease will be shown. We present work with functional network connectivity, an approach that enables the evaluation of the interplay between multiple networks and how they are affected in disease. We conclude by discussing new variants of ICA for extracting maximally group discriminative networks from data. In summary, it is clear that identification of brain networks and their inter-relationships with fMRI has great potential to improve our understanding of schizophrenia.

Keywords: fMRI, schizophrenia, independent component analysis, functional connectivity, functional network connectivity

BRIEF REVIEW OF FUNCTIONAL CONNECTIVITY

Functional magnetic resonance imaging (fMRI) has been used for almost 20 years, primarily to extract signals from brain regions that show blood oxygen level dependent (BOLD) changes in response to a cognitive task. More recently there has been increased interest in temporally coherent, but not necessarily directly task-correlated activity, derived from fMRI data. Early studies were performed using correlation of a seed region in sensorimotor cortex in rapidly sampled echo planar imaging (EPI) fMRI data and revealed a significant degree of low-frequency correlations with homologous contralateral regions (Biswal et al., 1995). These correlations, also present for visual and auditory cortices, appear to be related to both hemodynamic and neuronal activity (Biswal et al., 1997) mostly at lower frequencies (Cordes et al., 2001). Subsequently it was shown that whole brain data temporally sampled at a much lower rate also showed similar temporally coherent regions (Lowe et al., 1998).

Beyond correlation, multivariate methods based upon independent component analysis (ICA) have also been applied to measure functional connectivity, and have the advantage of not requiring explicit spatial priors or temporal filtering (McKeown et al., 1998). ICA was developed to solve problems similar to the "cocktail party" scenario in which individual voices must be resolved from microphone recordings of many people speaking at once (Bell and Sejnowski, 1995). The algorithm, as applied to fMRI, assumes a set of sparse, spatially independent brain networks, each with associated time courses. The model identifies latent sources whose elements (voxels) have the same time course and thus each component can be considered a temporally coherent network (TCN). We use the general term TCN to avoid a notion of state-dependence that pertains to resting state networks (RSN) and their particular instances such as the default mode network (DMN), as well as task-related networks computed from ICA (Calhoun et al., 2008a) and also embedded within maps of task-correlated activity (Sui et al., 2009b). Default mode is name given to one particular network which is found to show a signal decrease when a task is performed. This network is thus present to differing degrees at rest and during a task. A functionally connected network, by definition, has voxels which exhibit temporally coherent signal. These networks

appear to be largely robust and consistent, although they are also clearly modulated both spatially and temporally in the presence of a task (Calhoun et al., 2008a; Fransson, 2006; Sonuga-Barke and Castellanos, 2007).

Since the original observations, multiple studies have examined manipulations of tasks versus a resting baseline or evaluated changes in the correlations in clinical groups. There is some evidence that spatial maps reflecting TCNs may be more robust than those estimated during a standard approach based upon the general linear model (Calhoun et al., 2008b; Shehzad et al., 2009). ICA has been used to identify several TCNs present in healthy subjects either at rest (Beckmann et al., 2005; Damoiseaux and Greicius, 2009; Kiviniemi et al., 2003; Van de Ven et al., 2004) or during the performance of a task (Calhoun et al., 2001b, 2002; McKeown et al., 1998). There has also been interest in using TCNs as biological disease markers, e.g., TCNs have been used to distinguish mild cognitive impairment (Sorg et al., 2007) and Alzheimer's disease (Greicius et al., 2004) from healthy aging, schizophrenia from bipolar disorder (Calhoun et al., 2008b), or schizophrenia patients from unaffected first degree relatives and controls (Whitfield-Gabrieli et al., 2009).

A particular TCN that has received great interest is the DMN, that is believed to participate in an organized, baseline "idling" state of brain function that diminishes both during specific goal-directed behaviors (Raichle et al., 2001) and in inverse proportion to task difficulty (McKiernan et al., 2003). It is hypothesized that the default mode is involved in attending to internal versus external stimuli and is associated with the stream of consciousness, comprising a free flow of thought while the brain is not engaged in other tasks (Gusnard et al., 2001), however there are alternative explanations (Hampson et al., 2006). We reported recently an approach utilizing both the temporal lobe and default mode TCNs to differentiate schizophrenia, bipolar disorder, and healthy controls (Calhoun et al., 2008b). Other than these two TCNs, multiple others have been consistently identified (Beckmann et al., 2005; Kiviniemi et al., 2009) but have not been studied in detail for their relevance in schizophrenia so far. For clinical studies, the extraction of TCNs during task performance has been suggested as a way to constrain a participant's behavior beyond just "resting" while also stimulating the brain with a task that both patients and controls can perform accurately and which elicits robust brain function differences between the two groups (Calhoun et al., 2008b).

Collection of data during rest in subjects with neuropsychiatric disorders is a useful approach in several regards. First, ill participants are often unable or unwilling to perform tasks consistently in the scanner or to fully understand complex instructions – At rest, there are no such task demands. Second, abnormal task performance often occurs in schizophrenia, due to the cognitive disability associated with the disorder. This is often inevitably confounded with concomitant abnormal brain activation in a "chicken and egg" manner. This problem can be circumvented during resting state, thus potentially offering a clearer view of the underlying endophenotype (see accompanying article by Pearlson et al., in this issue). Finally, the occurrence of symptoms in the scanner, for example auditory hallucinations in schizophrenia, is usually thought of as undesirable "noise" during performance of a cognitive task but at rest may actually be contributing useful diagnostic information.

ORIGIN OF RESTING STATE CONNECTIVITY PATTERNS

Recall that the BOLD signal is a surrogate for neuronal activity. It is an indirect measure of neuronal activity after neurovascular transformation, and as such is not solely an index of localized electrophysiological processing in the brain volume but also mixed with global effects that affect blood oxygenation and flow, including variability of heart rate and respiration (Logothetis and Wandell, 2004; Raichle and Mintun, 2006). These physiological nuisance signals can yield oscillations in the low-frequency range (Wise et al., 2004), either due to aliased measurements and/or due to harmonics of their center frequencies in the range between 0.1 and 1 Hz, respectively. Since the initial observation of functional connectivity between regional fMRI time-series (Biswal et al., 1995) researchers have been aware of these confounds (Cordes et al., 2000). One way to estimate these effects is to acquire fMRI time-series at high sampling rates (~200 ms per volume) which avoids aliasing but which typically does not permit whole brain coverage. Where whole brain coverage is desired, heart rate and respiration can be measured inside the MR scanner and be used as nuisance covariates (Glover et al., 2000). Under the assumption that physiological nuisance affects the fMRI signal across the entire volume, global mean scaling has been a widely used processing step in functional connectivity analysis for denoising (Zarahn et al., 1997). Although this procedure effectively removes nuisance effects, one should be aware that it also alters functional connectivity patterns, and can yield artificially increased anti-correlations when seed-based correlation methods are used for analysis (Murphy et al., 2009). However, the observed anti-correlated networks are most likely not solely a consequence of preprocessing using global signal correction, since the global signal is not preferentially localized to these networks and the spatial distribution of negative correlations is not mandated by global scaling (Fox et al., 2009).

Note also that blind decompositions with ICA are less susceptible to this type of ambiguity (Birn et al., 2008; Fox et al., 2009) and show largely the same networks and anti-correlations between them (Damoiseaux et al., 2006; Kiviniemi et al., 2009). Additionally, several lines of evidence illustrate the neuronal nature of large-scale networks observable in the resting state and during task fMRI data. Although direct observations remain scarce and not necessarily yield consistent and stationary observations in electrophysiology and hemodynamics (Popa et al., 2009; Sirotin and Das, 2009), low-frequency neuronal activity patterns can account for slow fMRI fluctuations (Leopold et al., 2003; Shmuel and Leopold, 2008), and a network model of weakly coupled 40 Hz oscillators also shows low-frequency activity (Deco et al., 2009). For the DMN in particular, concurrent EEG-fMRI studies in humans show correlations between DMN and resting and event-related EEG features (Eichele et al., 2005; Laufs et al., 2003; Mantini et al., 2007; Scheeringa et al., 2008). There is also evidence that these resting networks may be coordinated by subcortical mechanisms (Uddin et al., 2008). In addition, structural and functional connectivity of the DMN appear tightly coupled (Hagmann et al., 2008; Skudlarski et al., 2008). These findings corroborate the multimodal description of the DMN in non-human primates (Vincent et al., 2007). One should also be aware of related psychophysiologic observations: heart rate and respiration are directly affected by cognitive and

affective states, which in turn are mediated by large-scale networks (Cacioppo et al., 2000; Critchley, 2005), such that excessive control for putative confounds might yield reduced sensitivity to detect plausible biological effects.

FUNCTIONAL CONNECTIVITY IN SCHIZOPHRENIA

Schizophrenia is a chronic, disabling mental disorder diagnosed on the basis of a constellation of 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 syndrome of neural circuitry leading to an impairment in the smooth coordination of mental processes, sometimes described as "cognitive dysmetria" (Andreasen et al., 1999).

Many researchers have examined the possibility of "disconnection" in psychiatric groups by analyzing brain function with functional connectivity methods (Bokde et al., 2006; Friston, 1995; Friston and Frith, 1995; Frith et al., 1995; Herbster et al., 1996; Josin and Liddle, 2001; Liang et al., 2006; Liddle et al., 1992; Mikula and Niebur, 2006). For example, in a sample of patients with schizophrenia, Liang et al. (2006), found disrupted functional integration of widespread brain areas, including a decreased connectivity among insula, temporal lobe, prefrontal cortex and basal ganglia and an increased connectivity between the cerebellum and other brain areas, during resting-state by analyzing correlations between brain regions. Similarly, Meyer-Lindenberg et al. (2001), reported pronounced disruptions of distributed cooperative activity in frontotemporal interactions in schizophrenia in selected regions of interest in positron emission tomography (PET) brain scans on working memory task. Other task-related studies reported a lack of interaction between right anterior cingulate and other brain regions (Boksman et al., 2005), disrupted integration between medial superior frontal gyrus and both the anterior cingulate and the cerebellum (Honey et al., 2005), as well as reduced functional connectivity in frontotemporal regions of subjects with schizophrenia (Lawrie et al., 2002). Disruptions in networks identified with ICA in large multisite studies have been shown for multiple tasks such as auditory oddball (Kim et al., 2009) and working memory tasks (Kim et al., In Press).

Because of their reliability, TCNs also appear to be ideally suited for use in diagnostic classification or prediction using machine learning techniques. Two TCNs have been of particular interest in schizophrenia (Bluhm et al., 2007; Calhoun et al., 2004; Garrity et al., 2007); one of which includes bilateral temporal lobe regions, which have previously been used to discriminate healthy controls from schizophrenia patients (Calhoun et al., 2004). A second TCN, one of the most studied, is the DMN (McKiernan et al., 2003; Raichle et al., 2001) discussed earlier.

Classification has been performed using fMRI data collected during an auditory oddball task for two patient groups as well as healthy controls. Component maps estimated using a group ICA approach (Calhoun et al., 2001a) were entered into two sample *t*-tests to evaluate pair-wise differences among the three groups. Results are presented for each group for two components, one in temporal lobe and also the default mode (**Figure 1**; left). We performed a multiple regression including the target, novel, and standard stimuli and the mean of the estimated beta parameters is shown in **Figure 1** (right). We were also able to utilize these results to accurately differentiate healthy controls, schizophrenia patients, and patients with bipolar disorder. This example illustrates the ability of group ICA to differentiate groups and also shows both a comparison of the spatial maps and the time courses.

FUNCTIONAL NETWORK CONNECTIVITY

Although studies identifying networks of regions through seed-based approaches or ICA help identify problems with typical functional integration among important brain regions, they do not typically examine patients to see if there is disruption in the relationship of activity between one large network of brain regions and another. However, schizophrenia patients may not only have deficits within networks, but also dysfunction between networks, in that their cognitive and behavioral deficits might be related to entire networks of regions failing to properly communicate with one another.

Related work on TCNs has discussed regions showing task-related increases and other regions showing task decreases, described as anticorrelated networks (Fox et al., 2005; Uddin et al., 2009). Kelly et al. (2008) presented evidence that competition between such task negative and task positive networks mediates behavioral variability during a flanker task while Popa et al. (2009) showed network differences in attentional modulation. Such networks have also been studied in schizophrenia subjects (Williamson, 2007) as well as their first degree relatives (Whitfield-Gabrieli et al., 2009).

The above approaches indicate growing interest in evaluating changes in the interactions between networks and how related changes in disease but, to date these have focused only on two, specific negatively correlated networks. However, we can study the interrelationship between multiple networks using an ICA approach, by examining group differences in the temporal relationship among components (Assaf et al., 2009; Jafri et al., 2008). Within a given component, the regions are by definition fully temporally coherent due to the ICA assumption of linear mixing (Calhoun et al., 2004). But as discussed earlier, one can focus not only on these time courses, but rather also on the weaker dependencies among components. The determination of functional temporal connectivity among components and the evaluation of group differences in these relatively weaker connections is defined as *functional network connectivity* (FNC) since the approach evaluates changes in the interrelationship between different brain networks (including multiple regions as opposed to correlating a single seed region of interest with other brain regions).

Jafri et al. (2008) evaluated differences in FNC of resting state TCNs in schizophrenia versus healthy controls by computing a constrained maximal lagged correlation. First ICA was performed on the fMRI data and seven networks were selected. The maximal lagged correlation (between −5 and +5 s) was then examined between all pair-wise combinations. The maximal correlation value and corresponding lag was saved. Correlation and lag values were calculated for all subjects and were later averaged for control and

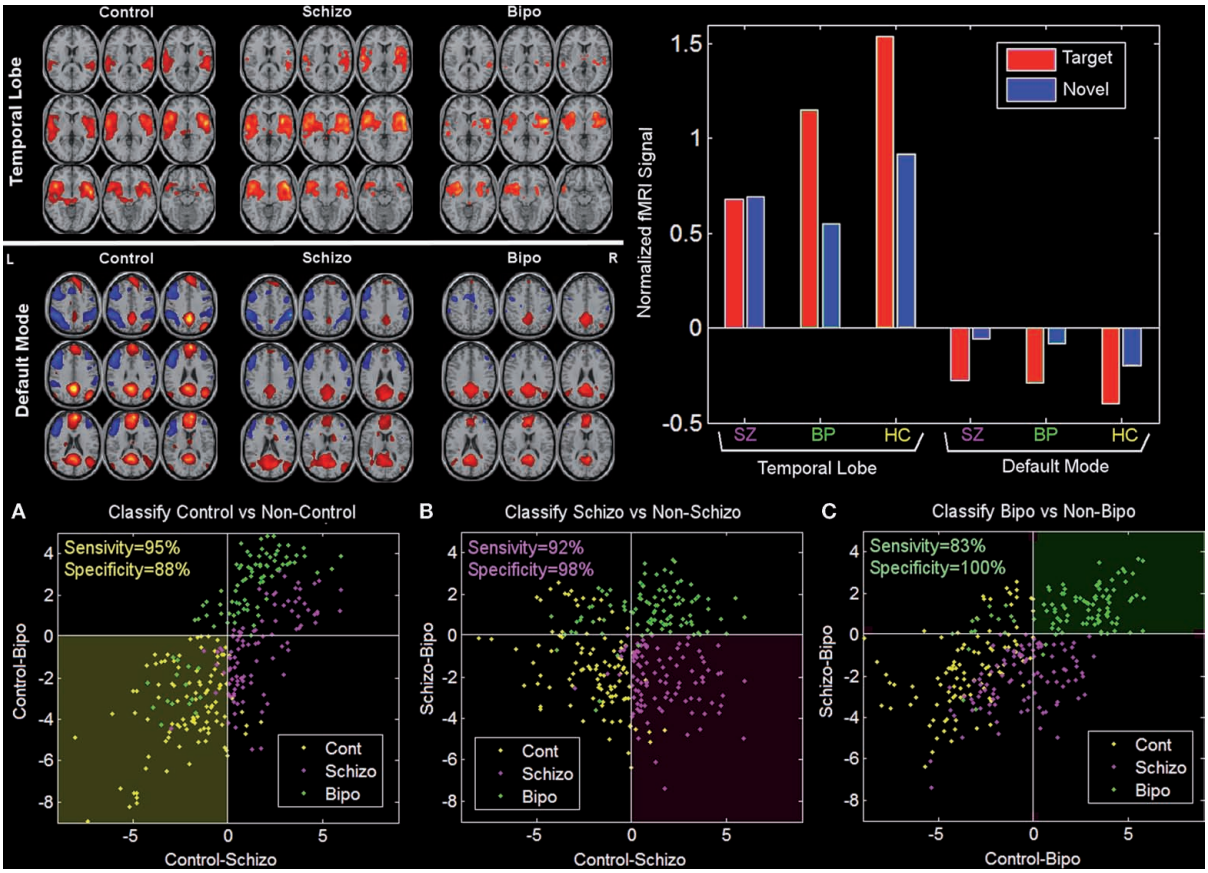

FIGURE 1 | Pair-wise comparisons of the control, schizophrenia, and bipolar groups (from Calhoun et al., 2008b). Two-sample *t*-tests were performed to illustrate most significant differences for each pair-wise comparison (top left). Note that these maps are generated from all subjects and actual classification regions will be slightly different due to the leave-1-out approach. On the top right is plotted the average beta weights for the stimuli broken out by group. On the bottom is shown a priori decision regions for three-way classification for **(A)** control (dark yellow) versus non-control (black), **(B)** schizophrenia (dark pink) versus non-schizophrenia (black), and **(C)** bipolar (dark green) versus non-bipolar (black). The actual diagnosis of a given individual is indicated by the color of the dot where controls are yellow, schizophrenia patients are pink, and bipolar patients are green. The classification was done on an independent data set each time using a leave-one-out approach. Sensitivity and specificity values were quite encouraging, with an average sensitivity (true positive) of 90% and an average specificity (true negative) of 95%.

patient group separately, where correlation values represented the dependency of two (out of seven) RSN on each other.

Five statistically significant differences in correlations values for patients versus controls were identified using a two sample *t*-test thresholded at $p < 0.01$, corrected for multiple comparisons using the false discovery rate (Genovese et al., 2002). Interestingly, patients showed considerably higher FNC than controls. **Figure 2** represents the significant correlation found among group differences. In the figure, a dotted line represents connectivity values for which patients had higher mean correlation than controls, while a solid line represents connectivity with higher correlation for controls. For example, components ***A*** and ***F***, which show significant correlation difference, are connected with a dotted line to indicate that patients had greater mean correlation values than controls for this connection.

Using a slightly different approach, where Granger causality was computed between networks, enables us to evaluate both the inter-network relationships and to identify which frequencies drive these relationships. Demirci et al. (2009) studied this for two different tasks, an auditory oddball task and a Sternberg working memory task. Different network structures showed aberrant FNC for the two tasks (see **Figure 3**).

In summary, the application of FNC to study schizophrenia appears to be a very powerful approach since it provides a way to study aberrant connectivity between sets of regions (networks), which is thought to be a core feature of schizophrenia.

FUSION OF NETWORKS (DATA FUSION OF MULTITASK/ MULTIMODAL NETWORKS)

In this last section we discuss methods which work at a group level to identify and combine multitask and multimodal networks. One promising approach is joint ICA, a second-level fMRI analysis method that has been used for capturing group-differences in two ways. These are (1) The contribution of one component to each group is dissimilar, which is reflected by the mean of mixing coefficients (quantified via *p* value of two sample *t*-test). (2) The back-reconstructed sources for each group are uncommon; namely, the component can vary spatially between two classes of populations as reflected by the joint histogram (quantified via *J*-divergence)

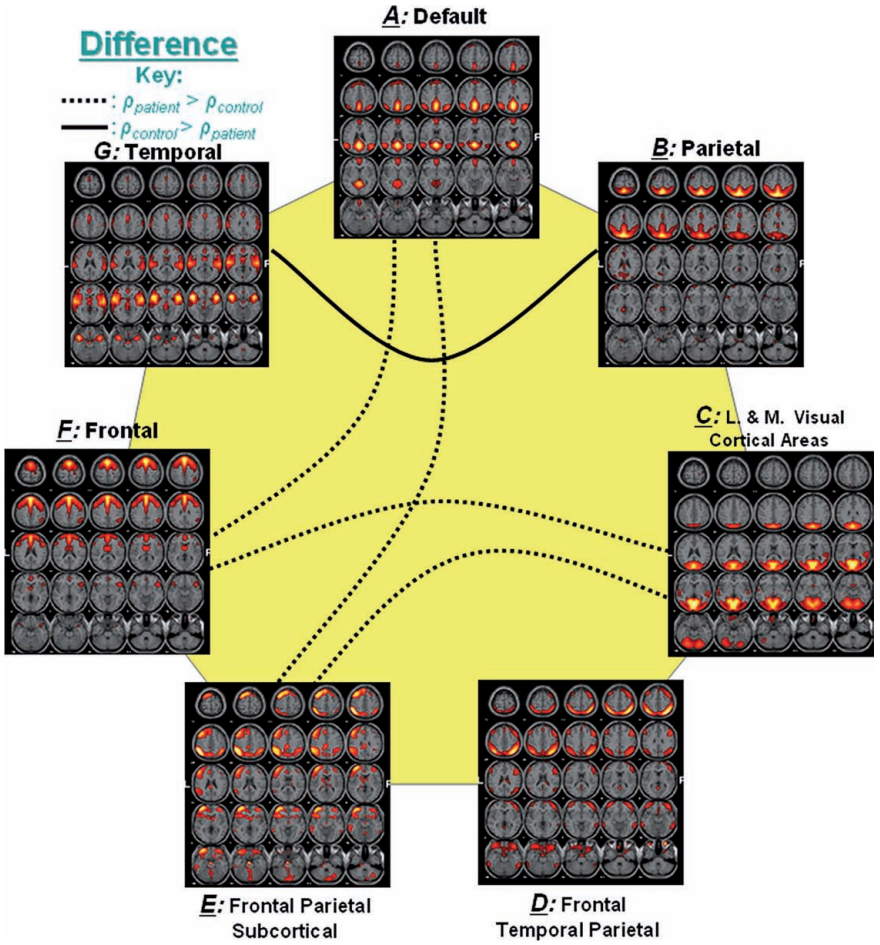

FIGURE 2 | Significant correlation between group differences (from Jafri et al., 2008). Out of 21 possible correlation combinations between seven components, only five combinations passed the two sample *t*-test ($p < 0.01$). The solid line represents the significant connectivity where controls have higher mean correlation than patients, while dotted line represents connectivity where patients have higher mean correlation. Presence of dotted lines rejects the hypothesis that controls should have more correlation between two components than patients.

(Calhoun et al., 2006a). We show three examples of this approach applied to schizophrenia.

MULTITASK fMRI

We performed a joint analysis of fMRI data collected from a Sternberg (SB) and an auditory oddball discrimination (AOD) task. Data in each task were collected from 15 controls and 15 schizophrenic patients. Additional details of the tasks and subjects are provided in (Calhoun et al., 2006b). A single joint component including regions in temporal lobe (for the AOD task) and dorsolateral prefrontal cortex (for the SB task) discriminated schizophrenia patients from healthy controls. A joint histogram was computed by ranking voxels surviving the threshold for the AOD and SB parts of the joint source in descending order and pairing these two voxel sets. Single subject and group-averaged joint histograms are presented in **Figures 4A,B** and the marginal histograms for the AOD and SB tasks are presented in **Figures 4C,D**.

In general, more AOD task voxels were active in the controls and the SB task showed a slight increase in standard deviation for the patients. Results also revealed significantly more correlation between the two tasks in the patients ($p < 0.0001$). A possible synthesis of the findings is that patients are activating less, but also activating with a less unique set of regions for these very different tasks, consistent with a generalized cognitive deficit. Essentially this suggests that schizophrenia patients demonstrate less modularity than healthy controls in the brain patterns induced in response to different tasks.

fMRI-sMRI

It is also feasible to use jICA to combine structural and functional features. Our approach requires acceptance of the likelihood of gray matter changes being related to functional activation. This is not an unreasonable premise when considering the same set of voxels (Thomsen et al., 2004), or even adjacent voxels (Meyer-Lindenberg et al., 2004) but also requires the acceptance of related gray matter regions and functional regions which are spatially *remote*. Given the functional interconnectedness of widespread neural networks, we suggest that this, also, is a reasonable explanation for the relationship between structural and functional changes.

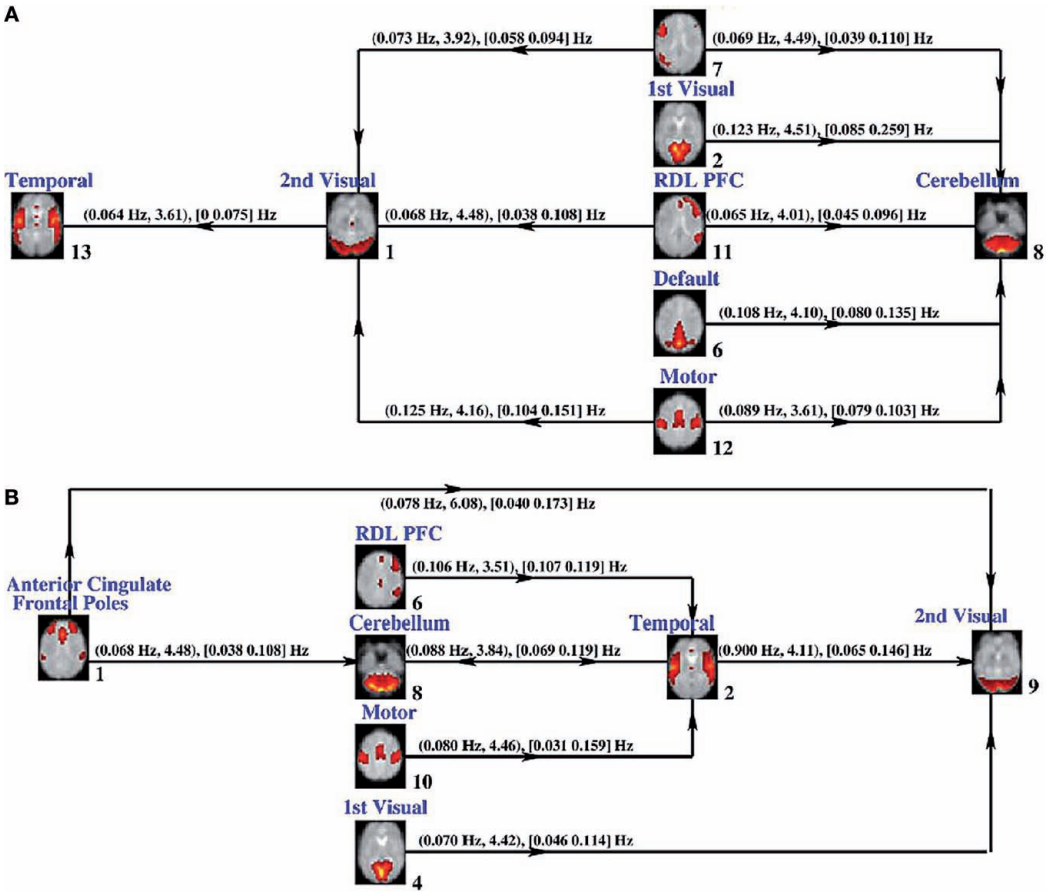

FIGURE 3 | Granger causality FNC results (from Demirci et al., 2009). Granger causality test results for SIRP data **(A)** and auditory oddball data **(B)**. The connections and their directions between brain networks are depicted along with (ft_{max}; t_{max}) frequency where maximum t-value is obtained and maximum t-value, [f_{min} f_{max}], frequency interval where the causal response is higher than 2, are given.

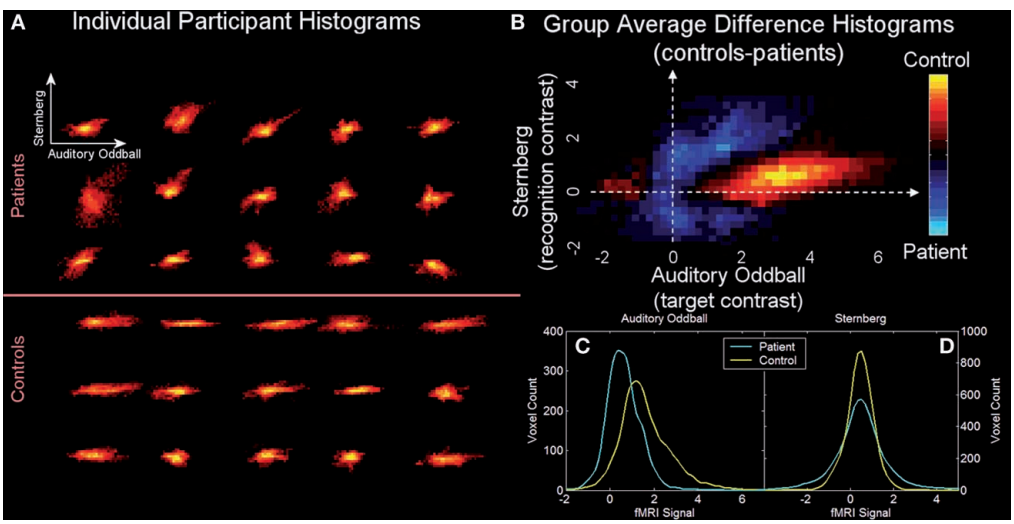

FIGURE 4 | Cross-task 2D histograms for AOD versus SB fMRI activation (from Calhoun et al., 2006b). Joint 2D histograms for voxels identified in the analysis. Individual **(A)** and group average difference **(B)** histograms (with orange areas larger in controls and blue areas larger in patients) are provided along with the marginal histograms for the auditory oddball (SPM contrast image for "targets") **(C)** and Sternberg (SPM contrast image for "recall") **(D)** data.

The next example is from a joint-ICA analysis of fMRI data of auditory oddball task and gray matter segmentation data (Calhoun et al., 2006a). Auditory oddball target activation maps and segmented gray matter maps were normalized to a study specific template in order to control for intensity differences in MR images based on scanner, template and population variations (Clark et al., 2001).

Results are presented in **Figure 5**. The AOD part of the joint source is shown in **Figure 5A**, the GM part of the joint source is shown in **Figure 5B**, and the ICA loading parameters separated by group and shown in **Figure 5C**. Only one component demonstrated significantly different loadings ($p < 0.002$) in patients and controls (loading for controls was higher than that for patients). The main finding was that the jICA results identified group differences in bilateral parietal and frontal as well as right temporal regions in gray matter associated with bilateral temporal regions activated by the AOD target stimulus. This finding suggests gray matter regions, in a different location than the functional changes, which may serve as a morphological substrate for changes in functional connectivity (Hagmann et al., 2008; Skudlarski et al., 2008).

fMRI-ERP

The feature-based jICA framework was used for fusion of event-related potential (ERP) and fMRI data collected from 23 healthy controls and 18 chronic schizophrenia patients, during the performance of an AOD task. Fifteen joint components were estimated from the target-related ERP time courses and fMRI activation maps via the jICA. One joint component was found to distinguish patients and controls using a two-sample *t*-test ($p < 0.0001$) on

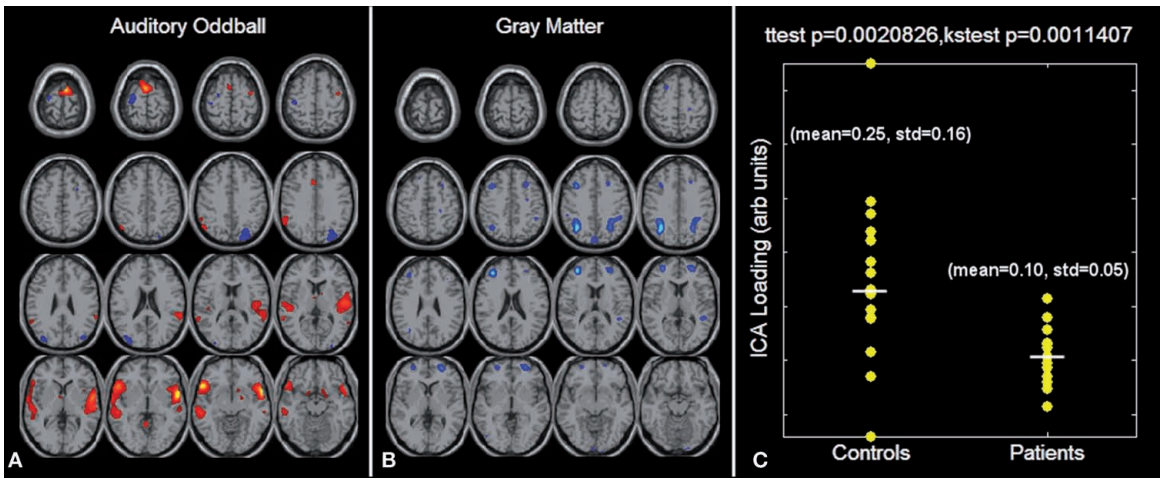

FIGURE 5 | Auditory oddball/gray matter jICA analysis (from Calhoun et al., 2006a). Only one component demonstrated a significant difference between patients and controls. The joint source map for the auditory oddball **(A)** and gray matter **(B)** data is presented along with the loading parameters for patients and controls **(C)**.

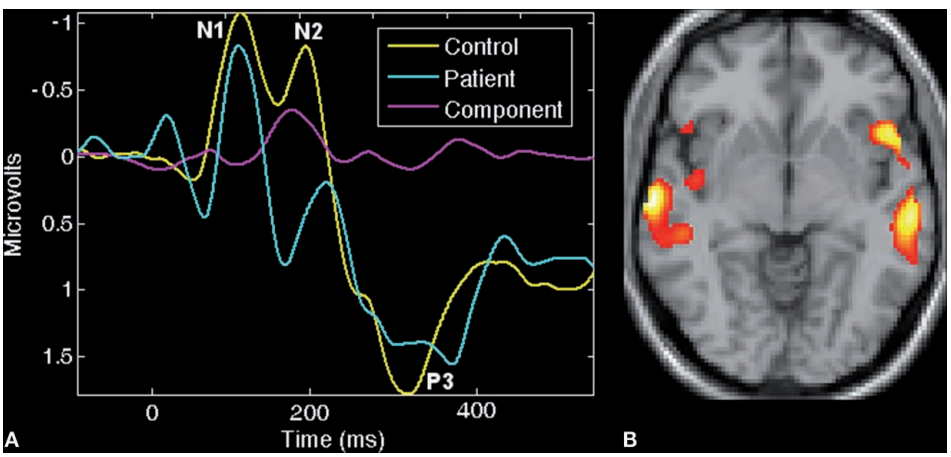

FIGURE 6 | ERP/fMRI jICA (from Calhoun and Adali, In Press). Joint component which showed significantly different loading parameters ($p < 0.0001$) for patients versus controls: **(A)** control (yellow) and patient (blue) average ERP plots along with the ERP part of the identified joint component (pink). **(B)** Thresholded fMRI part of the joint component showing bilateral temporal and frontal lobe regions.

patient and control loading parameters. This identified component showed a clear difference in fMRI at bilateral frontotemporal regions (**Figure 6B**) and in the ERP during the N2-P3 latency range (**Figure 6A**). Both the hemodynamic and electrophysiologic phenomena that were jointly expressed in this source have been previously implicated in schizophrenia.

In the same way as for **Figure 4** significant voxels/time points were used to generate an ERP vs fMRI histogram for controls (orange) and patients (blue), shown in **Figure 7**. The patients are clearly showing decreased activity in both fMRI and ERP data.

Note that jICA is a blind method that does not incorporate prior diagnostic information and is as such not optimized for detecting group differences. If the goal is to optimally identify potential biomarkers of disease, we can incorporate prior membership information and thus enhance the sensitivity of the method to detect relevant group differences. Towards this end, we have proposed a new framework combining coefficient-constrained ICA (CC-ICA)

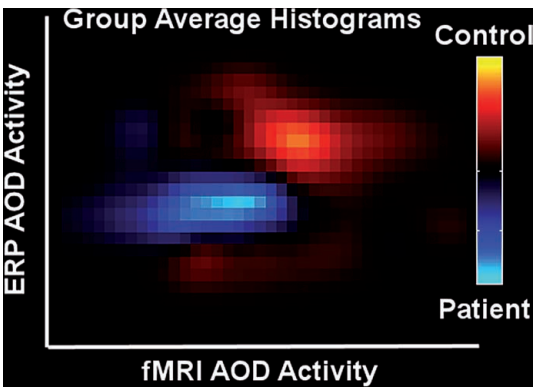

FIGURE 7 | ERP/fMRI histograms (from Calhoun and Adali, In Press). Joint histograms for patients (blue) and controls (orange).

(Sui et al., 2009a) and principal component analysis with reference (PCA-R) (Caprihan et al., 2008; Liu et al., 2008). This enhances the components' extraction sensitivity to group differences as well as their estimation accuracy. Secondly, a strength of the method is that it provides a unitary, and concise representation of a particular group discriminative feature from multimodal data in a single component. That is for each participant it summarizes many spatio-temporal features in a single loading parameter that can be associated with the probability of belonging to one or the other group. An analysis flow chart explaining how one proceeds from the raw data all the way to the final optimal components is given in **Figure 8**.

Coefficient-constrained ICA is formulated by incorporating a group difference criterion directly into the traditional ICA cost function to adaptively constrain the mixing coefficients of certain components to enhance group differences. CC-ICA aims to improve the components' extraction sensitivity to group differences as well as their estimation accuracy. The cost function is constructed as shown in Eq. 1, in addition to the traditional ICA objective function H for achieving independence; the sum of the squared T statistic of the constrained component(s) is added.

$$C = H + \lambda \cdot \sum T_i^2 \quad (1)$$

where λ is the constraint strength associated with the T^2 term, the suffix i represents index of the constrained ICs. The calculation of T_i and how to determine the constrained components including maximization of cost function C is based on the gradient algorithm are given in the original paper (Sui et al., 2009a).

The approach is applied to fMRI data from a sensorimotor (SM), auditory oddball (AOD) and Sternberg working memory (SBP) tasks collected in patients with schizophrenia and healthy controls. Three optimal components belong to two optimal feature combinations: two components extracted from the SM task alone, and one joint component from the SBP & AOD tasks. For display, the spatial maps of the three components were converted to Z-scores

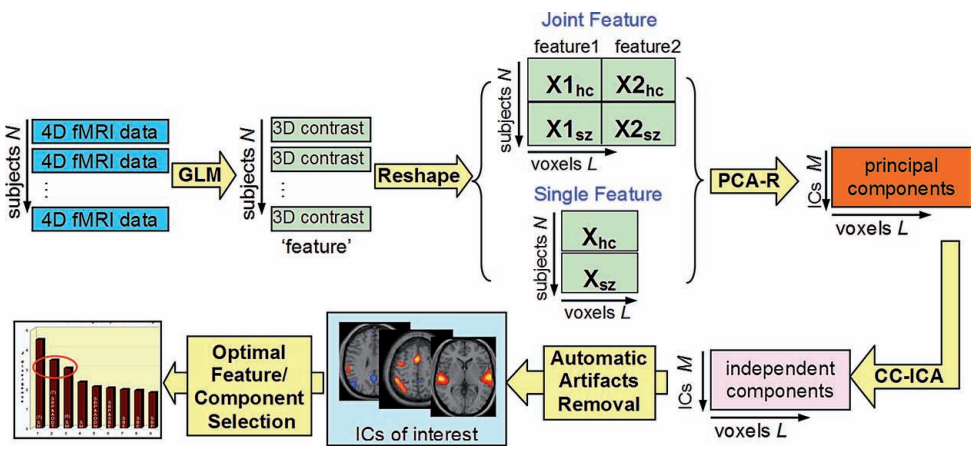

FIGURE 8 | An analysis flow chart showing the process of obtaining optimal group discriminative components (from Sui et al., 2009b). Flowchart of the optimal features/components selection, explaining how to determine the final optimal components from the raw data.

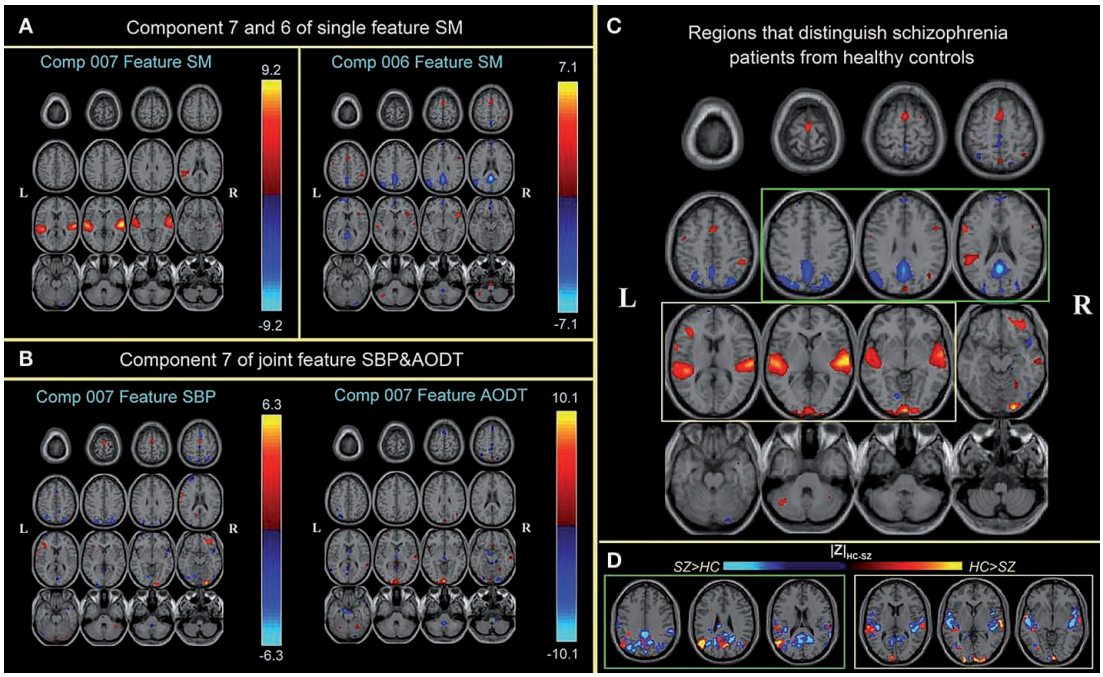

FIGURE 9 | Top three optimal components and the combined most group-discriminative regions (from Sui et al., 2009b). **(A,B)** are the spatial maps of the top three optimal components, which are converted to *Z*-scores and thresholded at $|Z| > 2.5$; **(C)** shows the overlapping regions of the four features with their original spatial map values, these activated regions are important for group discrimination and may serve as potential biomarkers of schizophrenia patients; **(D)** displays the difference between the back-reconstructed sources (HC-SZ) on the combined highlighted regions of the top three optimal ICs in (C), the regions where HC > SZ in $|Z|$ score are shown in orange, otherwise are shown in blue.

and thresholded at $|Z| > 2.5$ as shown in **Figures 9A,B**. **Figure 9C** gives a distinct view of the combined spatial maps in **Figures 9A,B**; these activated regions can best separate the two groups. A significant group difference is indicated in **Figure 9D** by subtracting the spatial maps of patients and controls. Orange indicates regions where controls have greater activity, blue regions indicate larger activity in patients.

The three optimal components predominantly describe aberrant patterns of activity in the superior temporal gyri, precuneus and angular gyri (DMN). Note also that each of these brain networks was identified separately in previous neuroimaging studies (Garrity et al., 2007; Kiehl et al., 2005; Tregellas et al., 2004). Our approach grouped them together in a framework that specifically identifies group discriminative features. Such a result cannot be obtained using traditional mass-univariate approaches which focus upon detection of activity differences in single voxels in single tasks, which is generally associated with lower sensitivity (Pereira et al., 2009). Moreover, the optimal components may only be "identifiable" through stimulation and comparison by different tasks, which further motivates a data fusion approach.

SUMMARY

In summary, the study of large-scale brain networks is becoming increasingly important, especially when studying complex mental illnesses like schizophrenia which impact many brain circuits. We have reviewed a number of approaches, mostly based upon ICA, which emphasize different aspects of the data. The brain is highly interconnected and many studies have focused upon aberrant connectivity as important in schizophrenia. However the brain is organized as networks involving multiple regions thus studying only how one region is connected to another is not going to provide a full picture of how this aberrant connectivity manifests. For example, two networks may be "intact" in that all the correct regions are present in both but interactions between these networks are aberrant. It is clear that utilizing methods which can capture information about brain networks as well as the interrelationship between networks is important. It is also clear that there is important information available for studies which contain a task as well as those that involve only rest.

There is still much work to be done, but it is encouraging to see the richness of network based analyses.

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Neurophysiological distinction between schizophrenia and schizoaffective disorder

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Schizoaffective disorder (SA) is distinguished from schizophrenia (SZ) based on the presence of prominent mood symptoms over the illness course. Despite this clinical distinction, SA and SZ patients are often combined in research studies, in part because data supporting a distinct pathophysiological boundary between the disorders are lacking. Indeed, few studies have addressed whether neurobiological abnormalities associated with SZ, such as the widely replicated reduction and delay of the P300 event-related potential (ERP), are also present in SA. Scalp EEG was acquired from patients with DSM-IV SA (n = 15) or SZ (n = 22), as well as healthy controls (HC; n = 22) to assess the P300 elicited by infrequent target (15%) and task-irrelevant distractor (15%) stimuli in separate auditory and visual "oddball" tasks. P300 amplitude was reduced and delayed in SZ, relative to HC, consistent with prior studies. These SZ abnormalities did not interact with stimulus type (target vs. task-irrelevant distractor) or modality (auditory vs. visual). Across sensory modality and stimulus type, SA patients exhibited normal P300 amplitudes (significantly larger than SZ patients and indistinguishable from HC). However, P300 latency and reaction time were both equivalently delayed in SZ and SA patients, relative to HC. P300 differences between SA and SZ patients could not be accounted for by variation in symptom severity, socio-economic status, education, or illness duration. Although both groups show similar deficits in processing speed, SA patients do not exhibit the P300 amplitude deficits evident in SZ, consistent with an underlying pathophysiological boundary between these disorders.

Keywords: schizophrenia, schizoaffective disorder, event-related potential, P300, EEG

INTRODUCTION

Kraepelin (1971) distinguished between "dementia praecox" and "manic-depressive psychosis" based on his observations that these two groups of psychotic patients exhibited different clusters of symptoms and courses of illness. This distinction has persisted in psychiatric nosology, underlying the current diagnostic categories of schizophrenia and major mood disorders. However, it has long been recognized that some patients exhibit symptoms from both diagnostic categories, fueling debate about how to classify them and where to draw the diagnostic boundaries between schizophrenia and psychotic mood disorders (i.e., bipolar disorder and psychotic depression). The term "schizoaffective psychosis" was first proposed by Kasanin (1933) to describe these patients and it has survived to the present.

Whether schizoaffective disorder is a distinct clinical entity (Tsuang, 1991; Kasanin, 1933; Kendler et al., 1995), a variant of schizophrenia (Williams and McGlashan, 1987; Evans et al., 1999) or major mood disorders (Lake and Hurwitz, 2007), or the reflection of an underlying continuum between them (Peralta and Cuesta, 2008), is still debated (Evans et al., 1999; Kempf et al., 2005; Cheniaux et al., 2008; Peralta and Cuesta, 2008). The issue is obscured by clinical heterogeneity within the schizoaffective category (Levitt and Tsuang, 1988), and its diagnostic unreliability among clinicians (Maj et al., 2000) and over time (Schwartz et al., 2000). Validation of the schizoaffective disorder construct as distinct from schizophrenia or bipolar disorder requires consideration of measurement domains other than the clinical data used to initially define the construct. Neurobiological measurement domains are perhaps most informative about whether distinguishing schizoaffective disorder from other psychotic and mood disorders successfully "carves nature at its joints." Unfortunately, research is sparse for most domains, non-existent for some, and findings have been inconsistent (Kempf et al., 2005; Cheniaux et al., 2008). For example, schizoaffective patients have better neurocognitive function than schizophrenia patients in some studies (Stip et al., 2005; Gruber et al., 2006; Heinrichs et al., 2008) but not others (Miller et al., 1996; Evans et al., 1999; Fiszdon et al., 2007). Perhaps because definitive data supporting a pathophysiological boundary between the disorders are lacking, schizoaffective and schizophrenia patients are often combined in schizophrenia research.

Among the measurement domains for which studies comparing schizoaffective disorder and schizophrenia are lacking are event-related brain potentials (ERP). In particular, despite the fact that amplitude reduction of the P300 component of the ERP is one of the most replicated neurobiological abnormalities in schizophrenia (Jeon and Polich, 2003), no studies have examined whether this biomarker is also compromised in schizoaffective disorder.

P300, a positive voltage deflection in the ERP occurring approximately 300 ms after stimulus onset, reflects neurophysiological processes associated with processing infrequent target, novel, or otherwise salient stimuli. P300 amplitude is thought to reflect attentional resource allocation (Isreal et al., 1980; Kramer and Strayer, 1988; Polich, 1989), phasic attentional shifts (Soltani and Knight, 2000), working memory updating of stimulus context (Johnson, 1986; Donchin and Coles, 1988), or stimulus salience (Sutton et al., 1965, 1967). Its latency is thought to reflect processing speed or efficiency during stimulus evaluation (Duncan-Johnson and Donchin, 1977).

Two subtypes of P300 are distinguished based on the type of deviant stimulus used to elicit it. P3b is the P300 elicited by infrequent task-relevant target stimuli in "oddball" tasks. It reflects top-down allocation of attentional resources to task-relevant events, and has a parietal scalp maximum. P3b amplitude reduction and latency delay in schizophrenia are established findings (Ford, 1999; Jeon and Polich, 2003). Cross-sectional studies often show P300 reduction to be associated with greater negative symptoms (Pfefferbaum et al., 1989; Mathalon et al., 2000a). In a longitudinal study, P3b amplitude tracked fluctuations in positive symptoms, although it remained abnormally reduced even when symptom severity diminished (Mathalon et al., 2000a). In addition, P3b is smaller and later in patients with longer illness durations (Mathalon et al., 2000b), suggesting it may also track illness progression. P3a is the P300 elicited by infrequent task-irrelevant deviant or distractor stimuli, which are typically either novel or otherwise salient, in oddball tasks. It reflects "bottom-up" orienting of attentional resources to these stimuli and has a fronto-central scalp maximum. Although few studies have examined P3a in schizophrenia, limited evidence suggests its amplitude is also reduced (Pfefferbaum et al., 1989; Mathalon et al., 2000a). In our longitudinal study, P3a also tracked clinical severity fluctuations but did not normalize when patients were most remitted (Mathalon et al., 2000a). Although not often directly compared, P300 abnormalities in schizophrenia are usually more prominent in the auditory than visual modality (Jeon and Polich, 2003).

Our primary aim was to examine whether P300 amplitude and latency elicited by target and task-irrelevant distractor stimuli in auditory and visual oddball tasks show differential sensitivity to schizophrenia. These four types of P300 (target vs. task-irrelevant distractor stimulus, auditory vs. visual modality) have never been directly compared within a single study of patients with schizophrenia. In addition to schizophrenia patients, we also recruited patients with schizoaffective disorder, providing an opportunity to assess whether they would show the same pattern of P300 abnormalities exhibited by schizophrenia patients.

MATERIALS AND METHODS

PARTICIPANTS

Electroencephalography (EEG) recordings were acquired from patients with schizophrenia (SZ; $n = 22$) and schizoaffective disorder (SA; $n = 15$), as well as healthy comparison subjects (HC; $n = 22$). All gave written informed consent after procedures had been fully described. Institutional Review Boards at the West Haven VA and Yale University approved this study.

Patients were recruited from community mental health centers and outpatient services of the VA Connecticut Healthcare System. Also, some patients were recruited by Dr. Hoffman to participate in a repetitive transcranial magnetic stimulation (rTMS) clinical trial for auditory hallucinations, in which case they were studied before initiating rTMS treatment. All but one patient were on stable doses of antipsychotic medications and met DSM-IV (American Psychiatric Association, 1994) criteria for schizophrenia or schizoaffective disorder based on a Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995). Patients with DSM-IV alcohol or drug abuse in the 30 days preceding the study were excluded.

HC subjects were recruited by newspaper advertisements and word-of-mouth, screened by telephone using questions from the SCID (First et al., 1995) non-patient screening module, and excluded for any history of Axis I psychiatric illness. All participants were excluded for significant head injury, neurological disorders, or medical illnesses compromising the central nervous system.

TASKS

In the 3-stimulus auditory oddball task, a random series of infrequent (15%) "target" high tones (1000 Hz), frequent (70%) "standard" low tones (500 Hz), and infrequent task-irrelevant distractor sounds (15%), were presented with a 1.25-s stimulus onset asynchrony. Distractor sounds were selected from a corpus of novel sounds developed by Friedman (Friedman et al., 1993). The tones were 50 ms in duration and 80 dB SPL (C scale). Distractor sounds ranged between 175–250 ms in duration and averaged 80 dB SPL (C scale).

In the 3-stimulus visual oddball task, an infrequent (15%) target stimulus (a plus sign, "+"), a frequent (70%) standard stimulus (a minus sign, "–"), and an infrequent (15%) distractor salient stimulus (a large blue square), were presented for 500 ms in a random sequence with a 1.25-s stimulus onset asynchrony.

In each task, subjects were asked to press a response key to the target stimulus. Each task comprised 3 runs of 100 stimuli, resulting in 45 targets, 45 distractor stimuli, and 210 standards for each modality.

MEASURES

EEG acquisition and pre-processing

Subjects sat in an acoustically shielded booth in front a computer monitor and wore insert earphones. EEG was recorded at 1000 Hz from 26 scalp sites, bandpass filtered between 0.05–100 Hz, and referenced to linked ears. Additional electrodes were placed at the outer canthi of both eyes and above and below the left eye to record eye movements and blinks (vertical and horizontal electro-oculogram [EOG]; VEOG, HEOG). All electrode impedances were maintained at or below 10 kOhm, with most EEG sites near 5 kOhm.

EEG data from 15 central sites were analyzed (F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6). Continuous data were separated into 1000 ms epochs time-locked to stimulus onset, with a 100-ms pre-stimulus baseline. VEOG and HEOG data were used to correct EEG for eye movements and blinks with a regression-based algorithm (Gratton et al., 1983). After baseline correction, epochs containing artifacts (voltages exceeding ±100 μV) were rejected.

Because P300s elicited by auditory and visual stimuli peak at different latencies, and because target P3b and distractor P3a have different topographies, different rules were used for identifying peaks. Auditory P300 was identified as the most positive peak in a 235–400 ms time window following stimulus onset, whereas visual P300 was identified within a 230–500 ms window. Target P3b peak was first identified at Pz, then a 50-ms window (±25 ms) surrounding this peak's latency was used to identify target P3b peaks at other sites. Distractor P3a showed more scalp variability in peak latency than target P3b, particularly at frontal sites, leading us to adopt a more flexible peak identification strategy. Distractor P3a peaks were first identified at all central and parietal sites. From the range of peak latencies obtained at central sites (T3, C3, Cz, C4, T4), minimum and maximum latencies were identified. By subtracting 50 ms from the minimum and adding 50 ms to the maximum, the search window for identification of P3a peaks at frontal sites was defined. The somewhat early latency cut-off (400 ms) for auditory P300s was chosen to avoid picking the second late positive component, which peaked around 550 ms (see **Figure 1**). Peak amplitudes were used for all P300 measures.

Clinical and demographic measures

Symptoms were rated by trained interviewers using the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987), yielding summary severity measures for all (PANSS General), positive (PANSS Positive) and negative (PANSS Negative) symptoms. Illness duration was calculated based on the age of illness onset estimate from the SCID. Parental socioeconomic status (SES) was assessed using the Hollingshead scale (Hollingshead and Redlich, 1958) with higher scores indicating lower parental SES. Demographic and clinical data for all groups are summarized in **Table 1**.

STATISTICAL ANALYSIS

Analysis of variance

Accuracy (percent correct) was analyzed in a 3-way Group (SZ, SA, HC) × Deviant Type (Target, Distractor) × Modality (Auditory, Visual) analysis of variance (ANOVA). Accuracy for distractor stimuli reflected withholding a response, such that a subject who never false-alarmed to distractor stimuli was 100% correct. Subject median reaction times (RT) to targets were analyzed in a 2-way Group × Modality ANOVA.

P300 amplitudes were analyzed in three ANOVAs, one for midline sites (Fz, Cz, Pz), and two for off-midline sites to assess for hemispheric laterality effects. The midline ANOVA included factors for Group (SZ, SA, HC), Deviant Type (Target, Distractor), Modality (Auditory, Visual) and Anterior-Posterior Site (AP: Frontal, Central, Parietal). The two off-midline ANOVAs each included factors for Group, Deviant Type, Modality, AP, and Hemisphere (Left, Right), but different lateral sites defined the

Table 1 | Sample demographic and clinical characteristics.

Variable and ANOVA Group effect *P*-value	Healthy control (HC) subjects *n* = 22				Schizophrenia patients (SZ) *n* = 22				Schizoaffective (SA) patients *n* = 15			
	Mean	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
Age (years) $p = 0.61$	37.29	12.62	23	59	39.95	10.75	22.00	56.12	36.46	10.05	21.35	54.99
Education (years)**** $p < 0.0001$; NC > SZ*, NC > SA*, SZ = SA	16.23	2.28	12.0	20.0	12.68	2.14	8.00	16.00	13.90	2.02	11.00	18.00
Average parental socioeconomic status $p = 0.43$	34.61	15.16	11.0	62.0	39.69	15.30	11.00	73.50	31.70	15.30	11.00	63.50
Mean symptom scores												
PANSS positive $p = 0.10$					17.15	4.37	12.00	25.00	15.00	4.77	7.00	25.00
PANSS negative $p < 0.06$					15.84	4.68	9.00	22.00	12.50	4.56	7.00	22.00
PANSS general $p = 0.03$ (SZ > SA)					33.63	8.00	20.00	54.00	27.53	7.21	17.00	42.00
PANSS anxiety $p = 0.69$					2.73	1.33	1.00	5.00	2.80	1.37	1.00	5.00
PANSS depression $p = 0.17$					2.79	1.22	1.00	5.00	2.20	1.21	1.00	5.00
PANSS hallucinations $p = 0.71$					3.87	1.93	1.00	6.00	3.66	1.23	1.00	5.00
PANSS delusions $p = 0.04$ (SZ > SA)					3.05	1.43	1.00	6.00	2.00	1.41	1.00	5.00
Handedness*****	19 right, 2 left, 1 ambidextrous				21 right, 1 left				14 right, 1 ambidextrous			
Gender	9 women, 13 men				5 women, 17 men				4 women, 11 men			
Diagnosis subtype***					3 Undifferentiated, 19 Paranoid				10 Depressed, 5 Bipolar			
Age at illness onset** $p = 0.29$					20.63	3.15	17.00	28.00	23.29	10.07	12.00	42.00
Duration of illness** $p = 0.12$					18.28	10.80	2.00	36.00	12.78	8.34	1.35	26.00
Antipsychotic medication type					18 atypical, 1 typical, 3 both				15 atypical			

*$p < 0.05$ with Scheffe test, **Missing data for 3 SZ and 1 SA patients, ***Missing subtype diagnosis for 2 SZ patients, ****Missing education data from 2 SA patients, *****Missing handedness data from 1 SZ patient.*

hemisphere effect in each ANOVA. In one, far lateral sites defined a Lateral Hemisphere factor (Lateral Left: F7, T3, P5; Lateral Right: F8, T4, P6). In the other, more medial off-midline sites defined a Medial Hemisphere factor (Medial Left: F3, C3, P3; Medial Right: F4, C4, P4).

P3b and P3a peak latencies for target and distractor stimuli were only measured at Pz and Cz, respectively, because that is where each type of P300 was largest and where its peak latency was likely to be most accurate. P300 latencies were analyzed in a 3-way Group × Deviant Type × Modality ANOVA.

Interactions were parsed using lower order ANOVAs. Differences between groups were assessed with least squares differences (LSD) *post-hoc* tests.

Hierarchical multiple regression

Relationships of P300 with clinical and demographic variables were evaluated using hierarchical multiple regression models in which P300 amplitude was regressed on the Clinical/Demographic Variable and Diagnosis (SZ versus SA) simultaneously entered into the model at Step 1, and the Diagnosis × Clinical/Demographic Variable interaction added to the model at Step 2. When the interaction, reflecting group differences in the slope of the P300-clinical/demographic variable regression line, was not significant, only regression results at Step 1 were considered, providing tests of (a) the relationship between the clinical/demographic variable and P300 and (b) diagnostic differences in P300 controlling for the clinical/demographic variable. These analyses were limited to target P3b measured at Pz and distractor P3a measured at Cz.

Mann–Whitney U-tests

Non-parametric Mann–Whitney *U*-tests were performed to compare P300 amplitudes in the SA-Bipolar Type ($n = 10$) and SA-Depressive Type ($n = 5$) subgroups. These tests were done separately for each modality and deviant type, using the Pz electrode for target P3b and the Cz electrode for distractor P3a. Non-parametric tests were deemed more appropriate than parametric tests for these analyses because of the small size of these two patient subgroups.

RESULTS

BEHAVIORAL DATA

Percent correct

ANOVA results are summarized in **Table 2**. There was a significant main effect of Group, with *post-hoc* tests showing that while SZ (94.4%) and SA (93.1%) groups did not differ, both were significantly ($p < 0.002$) less accurate than the HC group (98.5%). A significant Modality effect, which did not interact significantly with Group, indicated that subjects were more accurate during the visual (96%) than the auditory (94%) task. A significant Deviant Type effect indicated that subjects committed fewer false alarm errors to distractor stimuli than omission errors to targets. A significant Deviant Type × Group interaction was parsed with sub-ANOVAs within each group; the Deviant Type effect on accuracy was greater in the SZ (distractor: 98% versus target: 91%; $p = 0.02$) and SA (distractor: 95% versus target: 91%; $p = 0.04$) groups than in the HC group (distractor: 99% versus target: 98%; $p = 0.63$).

Reaction times to targets

As presented in **Table 2**, there was a significant Group effect, with HC (332 ms) responding more quickly than SZ (400 ms; $p < 0.001$) or SA (379 ms; $p = 0.01$) groups. RTs in the two patient groups did not differ ($p = 0.24$). Modality and Group × Modality effects were not significant.

ERP DATA

Group overlays of the grand average ERP waveforms and maps of their corresponding scalp topographies, in which the P300 component is evident as a large positive wave peaking around 300 ms, are shown separately for each Deviant Type and Modality in **Figure 1**. ANOVA results for P300 amplitude and latency conducted for midline electrodes, and results of the two off-midline ANOVAs assessing Medial and Lateral Hemisphere effects, respectively, are summarized in **Table 2**.

Midline analysis

There was a significant Group effect on P300 amplitude at midline sites (see **Table 2**). *Post-hoc* tests showed SZ to have smaller P300 amplitudes than either HC ($p < 0.0001$) or SA ($p < 0.001$) groups, but HC and SA groups did not significantly differ. Importantly, Group did not significantly interact with Deviant Type or Modality (see **Figure 2**).

A significant Modality effect on P300 amplitude indicated that visual P300s (12.8 μV) were larger than auditory P300s (8.6 μV). Deviant Type did not significantly affect P300 amplitude (target P300s = 10.5 μV; distractor P300s = 10.9 μV). Although the Modality × Deviant Type interaction was not significant, a significant higher-order Modality × Deviant Type × AP interaction emerged. To parse this interaction, the Deviant Type × AP interaction was assessed separately for auditory and visual modalities. Although the Deviant Type × AP interaction was significant in both modalities, it was stronger for auditory [$F(2,112) = 113.5, p < 0.0001$] than for visual [$F(2,112) = 52.6, p < 0.0001$] P300s. In both modalities, distractor stimuli elicited a P300 with a central maximum typical of P3a scalp topography, whereas target stimuli elicited a P300 with a parietal maximum typical of P3b topography (see **Figure 1**).

Off-midline analysis

Because schizophrenia patients sometimes have smaller P300s over left than right temporal sites (McCarley et al., 1991), our focus in the off-midline analyses was only on effects involving Group × Hemisphere interactions. None of these effects was significant for the medial or lateral hemisphere ANOVAs (see **Table 2**). Other significant hemisphere effects, which only emerged for the medial hemisphere sites, are not described further because they were not germane to our study aims.

P300 latency

There was a significant Group effect on P300 latency, with HC having an earlier P300 (333 ms) than SZ (355 ms) and SA (352 ms) groups (see **Table 2**). Significant main effects for Deviant Type and Modality indicated that P300 was later to target (361 ms) than distractor (333 ms) stimuli and later to visual (375 ms) than auditory (319 ms) stimuli, respectively. Group did not interact significantly with Deviant Type or Modality.

Table 2 | ANOVA summaries.

Source		Median RT		Percent correct		Median P300 latency	
	df	***F***	***p*-value***	***F***	***p*-value**	***F***	***p*-value**
Group	2,56	9.37	0.0001**	7.13	0.002***	3.90	0.03****
Deviant Type	1,56			13.3	0.001	26.90	0.0001
Deviant Type × Group	2,56			3.193	0.05	2.00	0.15
Modality	1,56	1.067	0.306	3.929	0.05	91.13	0.0001
Modality × Group	2,56	1.055	0.355	0.687	0.51	0.02	0.98
Deviant Type × Modality	1,56			0.017	0.90	1.01	0.32
Deviant Type × Modality × Group	2,56			0.273	0.76	0.13	0.88

Source		P300 Amplitude Midline Site Analysis (Fz, Cz, Pz)	
	df	***F***	***p*-value**
Group	2,56	9.11	0.0001
Deviant Type	1,56	0.89	0.35
Deviant Type × Group	2,56	1.48	0.24
Modality	1,56	69.47	0.0001
Modality × Group	2,56	1.36	0.27
AP*****	2,112	72.61	0.0001
AP × Group	4,112	0.91	0.44
Deviant Type × Modality	1,56	0.26	0.61
Deviant Type × Modality × Group	2,56	1.61	0.21
Deviant Type × AP	2,112	101.80	0.0001
Deviant Type × AP × Group	4,112	0.93	0.43
Modality × AP	2,112	9.93	0.0001
Modality × AP × Group	4,112	0.19	0.91
Deviant Type × Modality × AP	4,112	4.81	0.01
Deviant Type × Modality × AP × Group	4,112	1.13	0.35

Source		P300 Amplitude Medial Hemisphere Analysis (F3, F4, C3, C4, P3, P4)		P300 Amplitude Lateral Hemisphere Analysis (F7, F8, T3, T4, C5, C6)	
	df	***F***	***p*-value**	***F***	***p*-value**
Group	2,56	9.48	0.0001	7.59	0.001
Deviant Type	1,56	0.10	0.75	0.48	0.49
Deviant Type × Group	2,56	1.28	0.29	0.51	0.60
Modality	1,56	96.78	0.0001	79.90	0.0001
Modality × Group	1,56	1.79	0.18	0.53	0.59
AP	2,112	62.40	0.0001	40.06	0.0001
AP × Group	4,112	0.60	0.59	0.59	0.58
Hemisphere	1,56	12.31	0.001	2.86	0.10
Hemisphere × Group	2,56	1.20	0.31	1.48	0.24
Deviant Type × Modality	1,56	0.49	0.49	0.23	0.64
Deviant Type × Modality × Group	2,56	1.08	0.35	0.16	0.86
Deviant Type × AP	2,112	61.31	0.0001	20.48	0.0001
Deviant Type × AP × Group	4,112	0.87	0.46	0.62	0.60
Deviant Type × Hemisphere	2,112	14.54	0.0001	0.57	0.46
Deviant Type × Hemisphere × Group	4,112	0.94	0.40	1.54	0.22
Modality × AP	2,112	5.52	0.02	1.56	0.22
Modality × AP × Group	4,112	0.42	0.70	1.49	0.23
Modality × Hemisphere	1,56	0.05	0.83	0.11	0.74

(Continued)

Tables 2 | *(Continued)*

Source		P300 Amplitude Medial Hemisphere Analysis (F3, F4, C3, C4, P3, P4)		P300 Amplitude Lateral Hemisphere Analysis (F7, F8, T3, T4, C5, C6)	
	df	***F***	***p*-value**	***F***	***p*-value**
Modality × Hemisphere × Group	2,56	1.75	0.18	0.77	0.47
AP × Hemisphere	2,112	7.85	0.002	7.92	0.002
AP × Hemisphere × Group	4,112	0.44	0.72	0.29	0.83
Deviant Type × Modality × AP	2,112	14.70	0.0001	38.07	0.0001
Deviant Type × Modality × AP × Group	4,112	0.80	0.50	1.44	0.24
Deviant Type × Modality × Hemisphere	1,56	1.66	0.20	1.51	0.22
Deviant Type × Modality × Hemisphere × Group	2,56	1.18	0.31	0.57	0.57
Modality × AP × Hemisphere	2,112	9.93	0.0001	2.80	0.08
Modality × AP × Hemisphere × Group	4,112	0.11	0.96	0.51	0.68
Deviant Type × Modality × AP × Hemisphere	2,112	1.12	0.33	2.28	0.11
Deviant Type × Modality × AP × Hemisphere × Group	4,112	1.54	0.20	0.97	0.42

**Probability value based on Greenhouse-Geisser correction.*
***Group: HC < SZ (p = 0.005), HC < SA (p = 0.001), SZ = SA (p = 0.43), ***Group: HC > SZ (p < 0.0001), HC > SA (p = 0.01), SZ = SA (p = 0.24), ****Group: HC < SZ (0.01), HC < SA (p = 0.045), SZ = SA (p = 0.76), *****AP = Anterior-Posterior (frontal, central, parietal).*

P300 relationships with clinical and demographic variables

Results of hierarchical multiple regression analyses conducted to assess the effects of clinical or demographic variables, diagnosis (SZ versus SA), and their interaction, on P300 amplitude are presented in **Table 3**.

SZ patients had more severe symptoms than SA patients for PANSS General [$t(32) = -2.31$, $p = 0.028$], PANSS Positive Symptoms (trend level only: [$t(32) = -1.86$, $p = 0.072$], and PANSS Negative Symptoms [$t(32) = -2.09$, $p = 0.044$]. At step 2, no significant group differences in the slopes of the P300-PANSS Severity score relationships emerged for any of the P300s examined. At step 1, none of the PANSS Severity scores were significantly related to P300 amplitude, and SZ continued to exhibit smaller P300s than SA patients (significant Diagnosis effect) for all but the visual targets (which showed a trend).

The patient groups did not differ in illness duration [$t(31) = -1.58$, $p = 0.12$]. At step 2, the slopes of the relationship between illness duration and P300 amplitude significantly differed for the two groups only for P300 elicited by auditory target and visual distractor stimuli. The difference in slopes reflected relatively steeper declines in P300 amplitude with increasing illness duration in the SA group (auditory target P300: $r = -0.51$, $p = 0.06$; visual distractor P300: $r = -0.72$, $p = 0.004$) but not in the SZ group. As shown in **Figure 3**, larger P300 amplitude in SA, relative to SZ, patients was particularly evident early in the illness course. At step 1, P300s elicited by visual target and auditory distractor stimuli were not significantly related to illness duration. Moreover, SZ continued to exhibit smaller P300 than SA patients for auditory distractor stimuli, but not for visual targets (which showed a trend).

The patient groups had similar parental SES ($p = 0.25$). At step 2, the slopes of the relationship between parental SES and P300 amplitude were not significantly different for any of the types of P300. At step 1, parental SES was not significantly related to P300 amplitude. Controlling for parental SES, P300 amplitudes were smaller in SZ than SA patients for auditory target and visual distractor stimuli, with similar trends evident for visual target and auditory distractor stimuli.

The patient groups did not differ in years of education ($p = 0.12$). At step 2, the slopes of the relationship between education and P300 amplitude were significantly different in the two groups only for visual targets. This arose because in SA, but not SZ, patients, fewer years of education were associated with larger P300s. At step 1, this inverse relationship between years of education and P300 was evident in both groups for visual distractor stimuli, with a similar trend for auditory targets. Since these inverse relationships were somewhat paradoxical and are not relevant to our study aims, they are not discussed further. Importantly, after accounting for these education-P300 relationships at Step 1, P300 was still significantly reduced in SZ relative to SA patients.

When the 4 SZ patients taking typical antipsychotics were excluded, P300 amplitudes continued to be significantly smaller in the SZ than the SA group.

Comparison of schizoaffective disorder subtypes

Mann–Whitney *U*-tests comparing the SA-Bipolar Type ($n = 10$) and SA-Depressed Type ($n = 5$) subgroups found no significant group differences in P300 amplitude, regardless of which deviant type or sensory modality was examined.

DISCUSSION

This is the first ERP study to directly compare schizoaffective disorder and schizophrenia. Surprisingly, schizoaffective disorder patients did not exhibit abnormally reduced P300 amplitudes, despite significant P300 reduction in schizophrenia patients evident in both the present study and numerous prior studies (Ford, 1999; Jeon and Polich, 2003). This suggests that the neurophysiological mechanisms supporting attentional resource allocation to infrequent stimuli, whether they be task relevant targets or task-irrelevant distractors, are intact in schizoaffective disorder but impaired in schizophrenia.

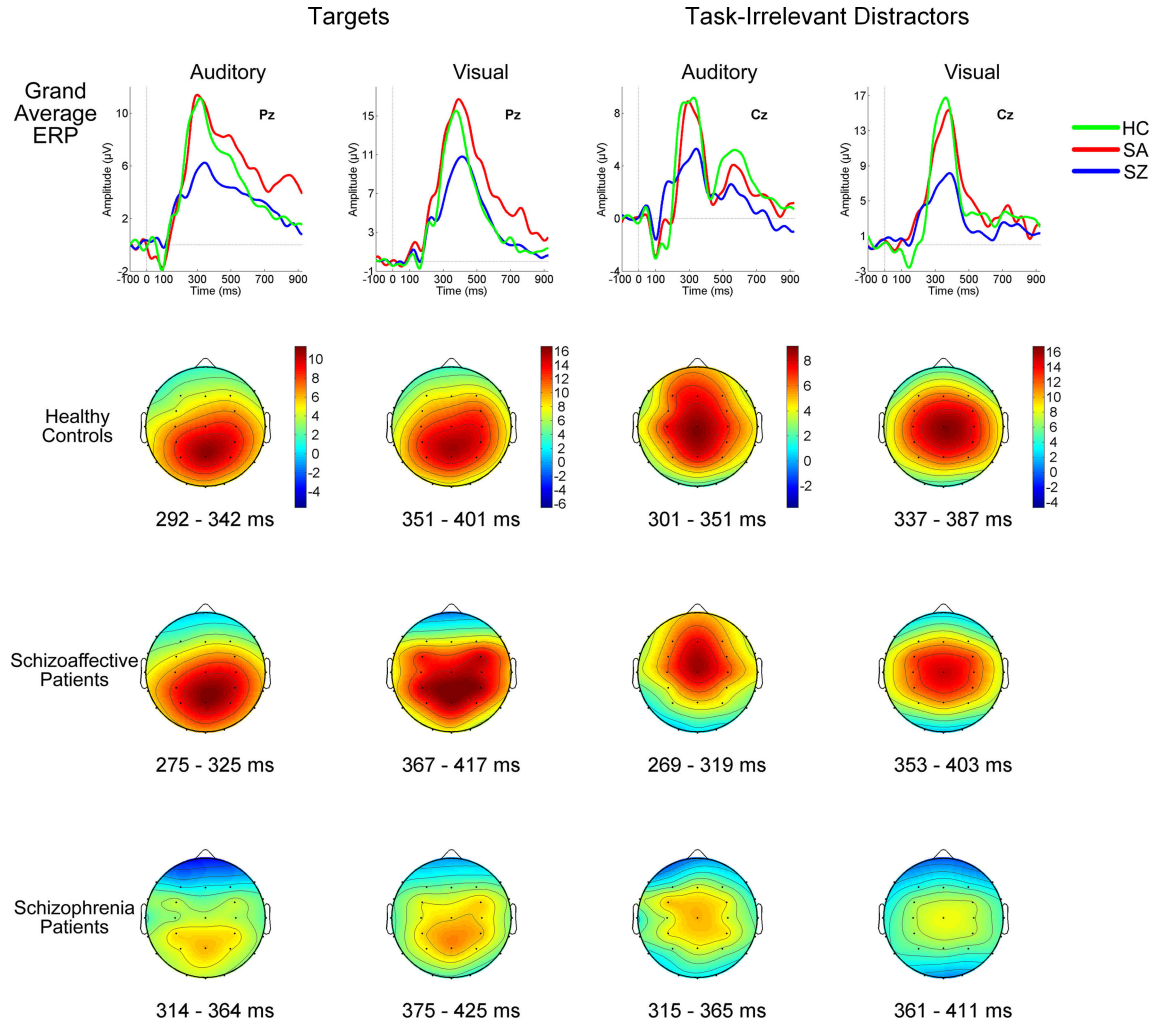

FIGURE 1 | Grand average ERPs (top row) and P300 scalp topography maps for Auditory and Visual Targets (far left and mid-left columns, respectively) and Auditory and Visual Task-Irrelevant Distractors (mid-right and far right columns, respectively) in healthy controls (HC; second row), patients with schizoaffective disorder (SA; third row) and patients with schizophrenia (SZ; fourth row). Latency windows capturing the P300 for each condition and group are indicated below each topographic map. The color-coding on the scalp topography maps reflects voltage for that group at that site. In the grand average plots, target ERPs are plotted from electrode Pz and task-irrelevant distractor ERPs are from Cz. ERPs are overlaid for HC (green tracings), SA (red tracings) and SZ (blue tracings) groups. Time is shown on the *x*-axis and voltage on the *y*-axis. Voltage scales are different for the different stimulus types. Positivity relative to the reference electrodes is plotted up.

This finding adds to a very sparse research literature examining neurobiological distinctions between schizophrenia and schizoaffective disorder (Evans et al., 1999; Kempf et al., 2005; Cheniaux et al., 2008; Peralta and Cuesta, 2008) and provides striking data in support of this distinction. In interpreting the P300 amplitude group differences observed in our study, it is important to note that the two patient groups showed similar deficits on speed and accuracy of responding and similar prolongation of P300 latency. They also had similar backgrounds in terms of education and parental socioeconomic status. Moreover, despite the tendency for the schizophrenia patients to have more severe symptoms than the schizoaffective disorder patients, the group differences in P300 amplitude persisted when these clinical and demographic measures were taken into account.

Although the groups did not differ in illness duration, the schizoaffective patients had particularly large auditory P3b and visual P3a amplitudes earlier in their illness course, relative to schizophrenia patients with similarly short illness durations. This is consistent with data showing schizoaffective disorder to be associated with a better premorbid adjustment than schizophrenia (Saracco-Alvarez et al., 2009). Subsequent P300 reduction due to illness progression appears to occur at a faster rate in schizoaffective disorder than in schizophrenia, at least for auditory P3b and visual P3a.

One of the hypotheses often subscribed to by clinical researchers is that the depressive type of schizoaffective disorder is more closely related to schizophrenia, whereas the bipolar type of schizoaffective disorder is more closely related to mood disorders. This distinction has received limited and somewhat inconsistent empirical support

from family studies and clinical outcome studies (Kendler et al., 1995; Cheniaux et al., 2008). This led us to examine whether the normal P300 amplitudes observed in the schizoaffective patients as a group obscured a P300 amplitude deficit evident only within the schizoaffective-depressed type subgroup. With the caveat that our analysis of this question was limited by the small sample size of the depressed type subgroup, the data from the present study showed no significant, or even trend level, difference in P300 amplitude between the two subtypes of schizoaffective patients.

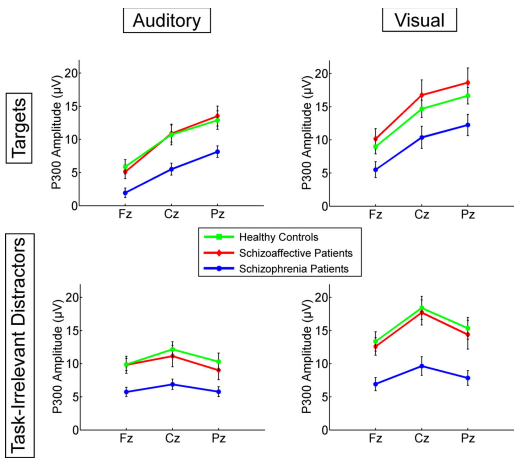

FIGURE 2 | Means for P300 amplitudes from Fz, Cz, and Pz are plotted for Auditory Targets (upper left), Auditory Task-Irrelevant Distractors (lower left), Visual Targets (upper right) and Visual Task-Irrelevant Distractors (lower right). Color-coding is the same as in **Figure 1.**

Although this is the first study to explicitly examine the difference in P300 between schizophrenia and schizoaffective disorder based on the application of current diagnostic criteria, prior studies by Strik et al. (1993) have documented normal or even enhanced P300 (Strik et al., 1997) amplitudes in patients who met criteria for cycloid psychosis, a psychotic disorder clinically distinguished from schizophrenia based on Leonhard's diagnostic classification system that has been influential in European psychiatry. The current findings are complementary to, rather than replicative of, Strik's earlier studies since cycloid psychosis is not clinically synonymous with current definitions of schizoaffective disorder (Vogl and Zaudig, 1985; Zaudig, 1990; Peralta et al., 2007). Nonetheless, both sets of findings underscore the fact that, despite the commonly held view that P300 amplitude reduction is a relatively non-specific electrophysiological abnormality observed in a number of psychiatric disorders, it may nonetheless be useful in demarcating or validating diagnostic boundaries within the clinical heterogeneity encompassed by chronic psychotic disorders. At least within these murky waters, P300 amplitude reduction may be relatively specific to schizophrenia. While the intact P300 amplitudes in observed in patients with schizoaffective disorder in the present study does not prove that

Table 3 | Multiple regression of P300 on clinical/demographic variables and diagnosis (schizophrenia versus schizoaffective disorder).

		Targets						Task-Irrelevant distractors					
		Auditory P300 (P3b) at Pz			Visual P300 (P3b) at Pz			Auditory P300 (P3a) at Cz			Visual P300 (P3a) at Cz		
Model	Regressor Variable	Step entered	Beta at step	*p*-value	Step entered	Beta at step	*p*-value	Step entered	Beta at step	*p*-value	Step entered	Beta at step	*p*-value
1	PANSS General (PG)	1	0.10	0.58	1	0.08	0.65	1	0.21	0.23	1	–0.18	0.28
	Diagnosis (DX)	1	–0.50	**0.007**	1	–0.35	0.067	1	–0.45	**0.016**	1	–0.40	**0.024**
	PG × DX	2	0.30	0.71	2	–0.10	0.91	2	–0.74	0.36	2	–0.47	0.54
2	PANSS Positive (PP)	1	0.21	0.21	1	0.13	0.48	1	0.05	0.78	1	0.05	0.78
	Diagnosis (DX)	1	–0.53	**0.003**	1	–0.36	**0.054**	1	–0.39	**0.036**	1	–0.48	**0.007**
	PP × DX	2	0.22	0.74	2	–0.05	0.94	2	0.00	0.99	2	–0.46	0.49
3	PANSS Negative (PN)	1	0.11	0.52	1	–0.03	0.86	1	0.09	0.62	1	0.07	0.69
	Diagnosis (DX)	1	–0.50	**0.006**	1	–0.31	0.10	1	–0.40	**0.031**	1	–0.49	**0.007**
	PN × DX	2	–0.13	0.84	2	0.11	0.88	2	0.90	0.17	2	0.19	0.77
4	Illness Duration (ID)	1	–0.18	0.27	1	–0.22	0.22	1	–0.14	0.42	1	–0.26	0.09
	Diagnosis (DX)	1	–0.44	**0.012**	1	–0.30	0.096	1	–0.41	**0.022**	1	–0.47	**0.005**
	ID × DX	2	0.83	**0.053**	2	0.67	0.15	2	0.23	0.61	2	0.91	**0.02**
5	Parental Socioeconomic Status (PSS)	1	–0.19	0.23	1	–0.31	0.061	1	–0.13	0.46	1	–0.13	0.41
	Diagnosis (DX)	1	–0.44	**0.009**	1	–0.29	0.080	1	–0.34	**0.054**	1	–0.50	**0.003**
	PSS × DX	2	–0.28	0.58	2	–0.40	0.31	2	0.03	0.96	2	–0.47	0.33
6	Years Education (YE)	1	–0.28	0.072	1	–0.14	0.40	1	0.07	0.66	1	–0.32	**0.03**
	Diagnosis (DX)	1	–0.60	**0.0003**	1	–0.44	**0.013**	1	–0.45	**0.009**	1	–0.65	**0.0001**
	YE × DX	2	1.39	0.14	2	2.22	**0.033**	2	–0.77	0.46	2	0.40	0.66

Bolded p-values indicate significant ($p < 0.05$) t-tests for beta coefficient at step entered.

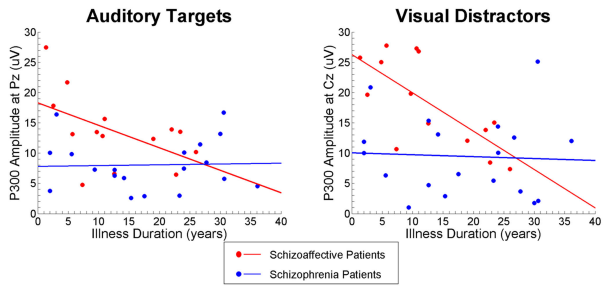

FIGURE 3 | Scatterplots showing relationships between Illness Duration (years) and P300 amplitude elicited by Visual Task-Irrelevant Distractors (right) and Auditory Targets (left) for schizoaffective patients (red) and schizophrenia patients (blue).

this disorder is pathophysiologically distinct from schizophrenia, it does raise questions about the wisdom of combining schizoaffective disorder and schizophrenia patients into a single group, a common practice in schizophrenia studies. Indeed, this practice may introduce neurobiological heterogeneity that obscures the distinct pathophysiologies of each disorder.

The initial aim of this study was to directly compare four types of P300, namely P3b and P3a elicited in auditory and visual oddball paradigms, in terms of their sensitivity to schizophrenia. While prior research suggests that auditory P300 is more sensitive to schizophrenia than visual P300 (Ford, 1999; Jeon and Polich, 2003), and that the top-down attentional processes reflected by target P3b may be particularly sensitive to schizophrenia's higher-order cognitive deficits relative to the bottom-up processes contributing to P3a, these conclusions are mainly derived from studies assessing only one or two of the P300 types assessed in our study. Surprisingly, direct comparison of all four types of P300 failed to support their differential sensitivity to schizophrenia. Instead, our results suggest that P300 is reduced and delayed in schizophrenia to the same degree, irrespective of the sensory modality and attentional system engaged.

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Is there a degenerative process going on in the brain of people with schizophrenia?†

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Schizophrenia is a biological and behavioural disorder which manifests itself in neurocognitive dysfunctions. The question of whether these key characteristics of the disorder are due to schizophrenia being a degenerative disorder has been discussed for more than 100 years. Neuropsychological data indicate that neurocognitive functions are relatively stable over time after illness onset. Several studies show that there is a decline in neurocognitive functioning prior to and in connection with onset of illness. There is no convincing evidence, however, that there is a progressive neurodegenerative process after onset of illness. Morphological data, on the other hand, indicate a degenerative process. Several novel longitudinal studies indicate a rapid reduction of vital brain tissues after onset of illness. In this paper some ideas about compensatory reactions and Cognitive Reserve Theory is outlined as possible explanations of the recent magnetic resonance imaging studies that show structural changes in the brain after the onset of schizophrenia, at the same time as cognitive functioning does not become more impaired. Determining whether schizophrenia is a neurodegenerative illness with progressive structural changes in the brain after debut of the illness, or a neurodevelopmental disorder starting in early life, is of significant importance for understanding the pathophysiology of the illness and its treatments.

Keywords: schizophrenia, neurocognition, degeneration, neurodevelopmental process, compensatory reactions

INTRODUCTION

Schizophrenia is a complex biological and behavioural disorder which manifests itself in neurocognitive dysfunctions. The question of whether these key characteristics of the disorder are due to schizophrenia being a degenerative disorder has been discussed for more than 100 years.

Before we go into the main theme of this paper, a clarification of a central concept might be necessary, namely degeneration. What characterizes a neurodegenerative process? The main issue is that brain tissue is destroyed. This usually includes cytopathology as well as neuronal and synaptic loss followed by gliosis, i.e. scar tissue development of the brain. It can also include programmed cell death, such as apoptosis, which does not lead to any scar tissue. Further, probably loss of isolated nerve cells may occur without gliosis. A degenerative process is the basis for most states of dementia. However, we must also be aware of the fact that a decrease in the brain volume (grey matter) occurs in healthy people, starting at the age of 15–20 years (Rapoport et al., 1999; Hulshoff Pol and Kahn, 2008). An important emerging research area is the role of glia cells in the regulation of neurodegeneration. A comprehensive treatment of this topic is beyond the scope of this paper. A review of this topic is to be found in Müller and Schwarz (2007).

Kraepelin (1919) was clearly of the opinion that schizophrenia is a degenerative disorder (dementia praecox). This view held stance until the middle of the last century. At that time some reports began to emerge that patients with schizophrenia could be cured through long term psychotherapeutic treatment or in some other way recover completely from the disorder. How could an illness be degenerative if it was possible to recover from it?

During the 1980 and 1990s several longitudinal studies of neurocognitive functioning in patients with schizophrenia began to emerge. These studies showed no evidence of decline in function over time. This was taken to indicate that there is no ongoing degenerative process in the brain, at least not after the onset of illness (Rund, 1998). Instead, a neurodevelopmental model emerged as the dominant explanatory framework for schizophrenia. According to this model normal brain development is disturbed by genetic or environmental factors in patients with schizophrenia. The model is supported by findings like higher prevalence of obstetric complications, minor physical anomalies, and neurological soft signs among people who later develop schizophrenia; as well as brain morphology findings that show smaller brain volumes even before the emergence of psychotic symptoms. The neurodevelopmental hypothesis was put forward as an alternative to the neurodegenerative hypothesis, although the two models do not stand in opposition to each other.

However, a few years ago the hypothesis of schizophrenia as a degenerative disorder re-emerged. This was primarily based on several new longitudinal magnetic resonance imaging (MRI) studies that showed substantial increases in the brains cavities (see next section), and corresponding excessive shrinkage of vital brain tissue, during the first years after the onset of illness. These studies

have led some to opine that the neurodegenerative hypothesis may have been overshadowed by the ascendancy of the neurodevelopmental hypothesis (Weinberger and McClure, 2005).

WHAT DO WE KNOW ABOUT STRUCTURAL CHANGES IN THE BRAIN OF PATIENTS WITH SCHIZOPHRENIA?

First of all, we have clear empirical support to state that there are changes occurring in the brains of patients with schizophrenia (Shenton et al., 2001; Harrison and Lewis, 2003; Weinberger and Marenco, 2003; Weinberger and McClure, 2005). The most robust findings seem to be that patients with schizophrenia have:

a. Larger ventricles than healthy controls. An increase in the lateral ventricle was found in 80% of the studies, while an enlarged third ventricle was found in 73% of the studies (Weinberger and Marenco, 2003). Seen together, 30 studies have found that patients with schizophrenia had 26% larger ventricles than healthy controls.
b. The volume of the frontal lobes is reduced compared to healthy controls. This was found in 59% of the studies. Parietal- and occipital lobe-abnormalities have also been found in several studies (Niznikiewicz et al., 2003).
c. There is a reduction in the volume of the temporal lobes, amongst other areas in the medial temporal lobe, which includes the amygdala–hippocampal complex and the neocortical temporal lobe. Temporal lobe reduction was found in 74% of the studies (Shenton et al., 2001).

However, it is primarily the fact that these changes in the brain seem to progress at rapid speed after the patient has become ill, at least the first years after the onset of illness, which has strengthened the hypothesis of an ongoing degenerative process. This has been shown in recent longitudinal studies including several first episode studies. In most of these studies structural brain changes have been found already at the time of onset of the psychosis. Pantelis and colleagues (Pantelis et al., 2003) found structural brain changes already prior to illness onset in high risk individuals. They found reduced grey matter in individuals who later developed a psychotic illness compared to those who did not. Gur et al. (1998) have also found clear indications that changes in the brain take place before the clinical symptoms emerge. While the early longitudinal studies did not indicate any progressive deterioration of the brain early in the illness (Weinberger and Marenco, 2003), the pattern is different in many of the more recent studies. Several of these studies showed dramatic structural changes over a relatively short time period:

– Chakos et al. (2005) showed that patients with schizophrenia had less hippocampal volume than age matched healthy controls and that the volume reduction was larger in older, than in younger patients.
– Jacobsen et al. (1998) documented a 7% reduction of the hippocampus per year.
– Rapoport et al. (1997) reported a 7% reduction of the thalamus per year in adolescents with schizophrenia. Further they found a 10% increase in ventricular volume per year. In a later publication the same research group (Rapoport et al., 1999) reported a significant reduction in grey matter in frontal and parietal areas in these adolescent patients over a 3- to 5-year period.
– Mathalon et al. (2001) showed that the left lateral ventricle increased by 13% a year, or a doubling of the size within an 8-year period.
– DeLisi et al. (1998) identified a clear reduction in hemispheric volume in 50 patients with first episode schizophrenia followed over a 4-year period.
– Sporn et al. (2003) found a substantial loss of grey matter through the teenage years in patients with early onset schizophrenia.
– Kasai et al. (2003) found a 9.6% progressive reduction in grey matter in the upper left temporal gyrus over a period of 1.5-year after the first hospitalization in patients with schizophrenia.
– Lawrie et al. (2002) showed a reduction in temporal lobe volume over a 2-year period in individuals at high risk who developed psychotic symptoms during this period.
– James et al. (2002) investigated early onset patients with schizophrenia and found enlarged lateral and third ventricle, in addition to a reduction in the left part of the amygdala. However, these researchers did not find further deterioration over a 3-year period.
– Cahn et al. (2002) found that the whole brain grey matter decreased during a 1-year follow-up of first-episode patients with schizophrenia.
– Ho et al. (2003) carried out a 5-year follow-up study of first-episode schizophrenia patients and found that the frontal white matter decreased.
– Jacob et al. (2005) followed the same prodromal cases as Lawrie et al. (2002) over another 3 years and confirmed their findings.
– Whitford et al. (2006) found grey matter reductions in first-episode patients with schizophrenia that were followed-up 2–3 years.

Taken together these studies indicate fairly comprehensive, multi focal structural changes in the brain over time in patients with first episode psychosis. Progressive volume loss seems most pronounced in the frontal and temporal areas. Progressive brain tissue loss in schizophrenia is, during a 20-year time period, found to be approximately twice that found in healthy people due to normal ageing (Hulshoff Pol and Kahn, 2008).

Another issue supporting a neurodegenerative hypothesis can be found in a study by Harvey et al. (1996). They found that in elderly patients with schizophrenia (above 65 years) there is a further reduction of neurocognitive functions beyond what would be expected from ageing. These results are based on a large patient sample. The findings of Harvey et al. (1996) may lead to speculation as to whether schizophrenia in some way makes the person particularly sensitive to the development of dementia in old age, or whether the brain in this group of patients is more sensitive to neurocognitive impairments as a response to normal age-related neurodegeneration (2003).

WHAT DO THE NEUROPSYCHOLOGICAL LONGITUDINAL STUDIES OF PATIENTS WITH SCHIZOPHRENIA SHOW?

The strongest argument against schizophrenia being a neurodegenerative disorder is the many longitudinal studies of neurocognitive functions that show that there is no worsening after the onset of

illness. Rather in general there seems to be some improvement in neurocognitive functioning, at least during the first period after the patients have gone into remission (Rund et al., 2006). It seems unlikely that a person can perform as well or better on various neuropsychological tests over time, if there is a simultaneously ongoing structural degeneration of the brain.

In 1998 Rund summarized the results of the 14 existing longitudinal studies of neurocognitive functioning in patients with schizophrenia (Rund, 1998). Only studies that had a follow-up time of at least 1 year were included in the analysis. It was concluded that after the onset of illness neurocognitive functioning is relatively stable over time. Kurtz (2004) have updated Rund's analysis with eight new longitudinal studies that have been published since 1997. Kurtz et al's results confirm the conclusion of Rund (Rund, 1998).

After this review article was published, Andreasen et al. (2005) have published results from a 9-year follow-up study. They show the same improvement in neurocognitive functioning that has been found in a number of studies the first years after the onset of illness. However, after 5 years the upward curve flattens out, and after 9 years the patients perform at the same level as they did at the first assessment.

Two studies with a 10-year follow-up time (Stirling et al., 2003; Hoff et al., 2005) show the same trend. Hoff et al. (2005) found no further reduction in neurocognitive functions over the first 10 years in patients that were assessed the first time at the onset of illness. However, they showed less improvement after 10 years than healthy controls on specific functions when controlling for differences between the groups at the first assessment. Hoff and colleagues concluded that patients remain relatively stable with regard to their level of neurocognitive functioning, at least through the first 10 years after the onset of illness.

Finally, these finding are confirmed and strengthened by a recent report from Øie et al. (2008). She has followed a group of early-onset schizophrenia over a 13-year period; a longer follow-up than in any other study. The main finding in this study is a significant decline in verbal memory and learning, and an arrest; i.e. lack of improvement, in attention and processing speed.

Beyond this general pattern of stability over the first years after illness onset, there is probably a certain fluctuation in level of functioning, particularly in functions that are state related (i.e. influenced by clinical state). In one study Rund et al. (1997) investigated 15 patients with schizophrenia with a battery consisting of 10 neuropsychological tests in two distinct different phases; an acute phase and a remission phase. We found a clear tendency that patients performed better when they were in remission. This may indicate that the psychotic experiences/symptoms themselves make it more difficult to concentrate on the test, something which is necessary to perform well. It is difficult to know whether it is the fact that the psychotic symptoms disappear that makes the patient also perform better on neuropsychological tests, or whether the improvement is caused by other factors, such as for instance the direct chemical effect of medication.

What else, in addition to the longitudinal studies of neurocognitive functioning, goes against schizophrenia being a degenerative disorder? Several biological "markers" appear to do so. First of all, there is no evidence of gliosis in schizophrenia (Woods, 1998), which is a sign of degeneration (see Section "Introduction"). Also, in post mortem studies there is no consistent evidence of degenerated neurons, cellular changes, loss of cell embryos, or molecular changes (Weinberger and Marenco, 2003).

A third argument against schizophrenia being a degenerative disorder is the fact that many patients show clinical improvement over time. In several of the longitudinal MR-studies (Rapoport et al., 1997; DeLisi et al., 1998; Gur et al., 1998; Jacobsen et al., 1998) the patients showed clinical improvement during the same time period that large structural changes took place in the brain. As Weinberger and Marenco (2003) pointed out, clinical improvement is hardly what one would expect as a result of progressive loss of brain tissue. This is, however, a more likely combination than performing as well on neuropsychological tests over time, while at the same time loosing brain tissue. Actually, Sporn et al. (2003) found that a greater degree of clinical improvement was significantly related to a reduction in grey matter.

WHEN DO THE COGNITIVE IMPAIRMENTS EMERGE?

There is no doubt that neurocognitive impairments are evident at the onset of illness in most patients who develop schizophrenia. However, we must also be aware that 35–40% of the patients do not have a significant impairment in neurocognitive functioning (Rund et al., 2006); i.e. they function within what must be characterized as the normal range (some healthy controls also function below average). Nevertheless, patients functioning within the normal range may have had a reduction in neurocognitive functioning after they became ill. Also several studies of high risk groups have found that these individuals show signs of neurocognitive deficits many years prior to the onset of illness (Jones et al., 1994; Cornblatt et al., 1999; Cannon et al., 2000; Fuller et al., 2002; Niendam et al., 2003; Ang and Tan, 2004). Moreover, several prodromal studies indicate that the neurocognitive impairments evident after the psychotic breakthrough are also evident prior to the onset of illness (Caspi et al., 2003; Gschwandtner et al., 2003; Wood et al., 2003; Hawkins et al., 2004; Brewer et al., 2005). Probably there is a further reduction in neurocognitive functioning just prior to the first psychotic episode (Caspi et al., 2003). A preliminary conclusion is that precursors to the cognitive deficits are evident relatively early, that these develop gradually and that they are found in corresponding form and approximately the same degree in the prodromal phase, as in remission. The psychotic experiences or symptoms exacerbate the neurocognitive deficits somewhat during the acute phase. Such a development with an early insult in the neural development that remains for the duration of life, but that does not get worse over time, may best be characterized as a static encephalopathy (Rund, 1998).

HOW CAN THE CONTRADICTORY FINDINGS FROM MORPHOLOGICAL AND NEUROPSYCHOLOGICAL STUDIES BE EXPLAINED?

There is no doubt that there is a "deterioration" of most neurocognitive functions in patients who develop schizophrenia. But much of this seems to occur prior to the onset of illness. We also have reason to believe that this neurocognitive deterioration to some degree runs parallel with structural changes in the brain. If one chooses to use the term neurodegeneration about what happens prior to the onset of illness, there is evidence suggesting that

schizophrenia is a degenerative disorder. But this is not the regular use of the term degeneration, nor was this how Kraepelin used the term. With his "dementia praecox" term he was referring to the assumption that there is a progressive worsening of the condition after the onset of illness.

We cannot provide a definite answer as to whether schizophrenia is a degenerative disorder (in the sense of a progressive degenerative state after the onset of illness). Longitudinal studies of neurocognitive functioning provide a relatively consistent indication that the impairment does not progressively worsen the first years after the onset of illness. However, some longitudinal studies with a very long follow-up period indicate that there is a certain decline after many years of illness. This may be due to medication or other biological effects. The decline may also be caused by under-stimulation from the environment. (Such under-stimulation may also to a certain degree explain the structural changes evident in the brains of patients with schizophrenia.) In essence, we need to realize that the morphological data to a great extent are inconsistent. There are no two studies that have found the exact same structural changes in this patient group (Weinberger and McClure, 2005).

How can we then explain more recent MRI studies that show clear cut structural changes in the brain after the onset of illness, at the same time as neurocognitive functioning does not become more impaired? Two issues can be pointed out:

The first issue may be what Lieberman (1999) amongst others has suggested, i.e. that there may be two ongoing pathogenic processes in schizophrenia; one neurodevelopmental process and a limited neurodegenerative or neuroprogressive process. McGlashan and Hoffman (2000) suggest that such neuroprogressive processes are a developmentally determined reduction in the connections between cortical synapses. (If we emphasize the fact that post mortem studies first and foremost show loss in neuropil and not in nerve cells in the cortex in patients with schizophrenia, the term neuroprogressive is more adequate than neurodegenerative). In Gur et al.'s (1998) study for instance, they only identified a sub-group of patients that showed progressive structural change after the onset of illness. Thus, it is possible that there are at least two types of schizophrenia; one with a good prognosis and one with a poorer prognosis and a clearer biological basis. This would mean a return to a hypothesis which has been of great interest throughout the history of schizophrenia research (see, for instance, Murray et al., 1992).

A second issue concerns the plasticity in the human brain. DeLisi et al. (1998) have for instance showed that the size of the ventricles may alternatively increase, decrease, then increase again over such short time periods as months. In the previously referred study by Lawrie et al. (2002), they found the same reduction in ventricular volume in healthy controls as in the high risk group that developed psychotic symptoms. It is also likely that the brain compensates for some of the loss that occurs in nerve cells or neuropil.

Animal studies indicate that damage to the brain may illicit compensatory reactions such as synaptic growth. It is also possible that new cells may develop in the human brain. Stern (2002) suggests that the brain actively attempts to cope with, or compensate for, pathology. The idea of reserve against brain damage stems from the repeated observation that there does not appear to be a direct relationship between degree of brain damage and the clinical manifestation of that damage. Cognitive Reserve Theory explains why individuals evidence different neuropsychological deficits following the same neurological damage. Cognitive reserve may be based on more efficient utilization of brain networks or of enhanced ability to recruit alternate brain networks as needed.

There are several possible alternative models that may explain the brain changes occurring after the onset of illness: It could be degeneration occurs with varying degrees of compensation or it could be that there are regressive processes that are undetectable in macroscopic investigations of the brain. It is also possible that there is a reorganization of synaptic connections without any form of degeneration or regression. Further, it could be that the brain more efficiently utilizes brain networks or enhances the ability to recruit alternative brain networks as needed, as Cognitive Reserve Theory suggests.

Still another possibility is that brain structural or volumetric changes affect certain sub-groups of patients more than others. A complicating matter could, however, be the heterogeneity of schizophrenia and individual variation regarding both functional and structural brain measures. In a recent meta-analysis of MR volumetric changes in schizophrenia and bipolar disorders, compared to healthy controls (Arnone et al., 2009), it was found that schizophrenia patients differed from bipolar patients with more regional structural changes compared to global changes in bipolar disorder patients. Implicated regions were enlargement of the lateral ventricles, pointing to frontal and temporal volumetric reductions in schizophrenia, and reduction of amygdale volume (Arnone et al., 2009). In addition, Kalus et al. (2004) reported reduction of hippocampal volume in patients with schizophrenia, which was related to alterations in white matter coherence between hippocampal sub-structures. In particular the hippocampal alterations could be related to the psychopathology of schizophrenia that could be more critical for sub-groups of patients with clearly defined cognitive impairments. It is therefore possible that previous studies of neurodegeneration have not paid enough attention to the symptomatic heterogeneity of the disorder, and that this could be related to brain structural changes over time, pointing to a possible degenerative process.

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The functional consequences of cortical circuit abnormalities on gamma oscillations in schizophrenia: insights from computational modeling

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Schizophrenia is characterized by cortical circuit abnormalities, which might be reflected in γ-frequency (30–100 Hz) oscillations in the electroencephalogram. Here we used a computational model of cortical circuitry to examine the effects that neural circuit abnormalities might have on γ generation and network excitability. The model network consisted of 1000 leaky integrate-and-fire neurons with realistic connectivity patterns and proportions of neuron types [pyramidal cells (PCs), regular-spiking inhibitory interneurons, and fast-spiking interneurons (FSIs)]. The network produced a γ oscillation when driven by noise input. We simulated reductions in: (1) recurrent excitatory inputs to PCs; (2) both excitatory and inhibitory inputs to PCs; (3) all possible connections between cells; (4) reduced inhibitory output from FSIs; and (5) reduced NMDA input to FSIs. Reducing all types of synaptic connectivity sharply reduced γ power and phase synchrony. Network excitability was reduced when recurrent excitatory connections were deleted, but the network showed disinhibition effects when inhibitory connections were deleted. Reducing FSI output impaired γ generation to a lesser degree than reducing synaptic connectivity, and increased network excitability. Reducing FSI NMDA input also increased network excitability, but increased γ power. The results of this study suggest that a multimodal approach, combining non-invasive neurophysiological and structural measures, might be able to distinguish between different neural circuit abnormalities in schizophrenia patients. Computational modeling may help to bridge the gaps between post-mortem studies, animal models, and experimental data in humans, and facilitate the development of new therapies for schizophrenia and neuropsychiatric disorders in general.

Keywords: schizophrenia, computational model, gamma oscillation, cortical excitability

INTRODUCTION

A considerable body of evidence has been amassed from post-mortem brain samples that schizophrenia is associated with particular abnormalities of neural microcircuits. At the same time, our knowledge of the abnormalities of brain function and macroscopic anatomy in schizophrenia has expanded considerably. What is needed now is an integration of findings across these different domains. Towards this end, we constructed a simple computational model of a small cortical area with which we could simulate γ-frequency (30–100 Hz) synchronization. We then examined the effects of schizophrenic neural circuit abnormalities on the γ oscillation and network excitability. Our goal was to determine if reduced synaptic connectivity, reduced inhibitory neurotransmission, and NMDA receptor hypofunction could be detectable with non-invasive measures, so that it might be possible to infer which types of neural circuit dysfunction might be present in schizophrenia patients.

Neural synchronization in the γ band has been proposed to mediate the formation and selection of cell assemblies in local and distributed circuits (Singer, 1999). Synchronous γ oscillations emerge in a network from the interplay between pyramidal cells (PCs) and interneurons (Borgers and Kopell, 2005; Oren et al., 2006). One class of inhibitory interneuron appears to be particularly important for mediating γ oscillations: the perisomatic-targeting, fast-spiking interneurons (FSIs) that express the calcium-binding protein parvalbumin (PV) (Bartos et al., 2007). This class includes chandelier and basket cells, which make γ-amino-butyric-acid type A ($GABA_A$) synapses onto their targets, and also synchronize each other through gap junctions. In schizophrenia PV interneurons show evidence of decreased GABA synthesis, suggesting a specific link between this disorder and the neural/cognitive functions associated with γ oscillations (Gonzalez-Burgos and Lewis, 2008; Uhlhaas et al., 2008).

Supporting this hypothesis, reductions of γ oscillation power and/or phase synchronization in the scalp-recorded electroencephalogram (EEG) have been observed in schizophrenia patients, for example in the auditory (e.g., Light et al., 2006; Spencer et al., 2008b, 2009) and visual (e.g., Spencer et al., 2008a) sensory modalities; in corollary-discharge processes in the motor system (Ford et al., 2008); and in the prefrontal cortex in association with cognitive control processes (Cho et al., 2006). Furthermore, correlations have been found between oscillation measures and schizophrenia symptoms such as hallucinations, disorganization, thought disorder, and attention deficits (Spencer et al., 2004, 2008b), avolition/apathy (Ford et al., 2008), and working memory (Light et al., 2006).

As a complementary measure we examined network excitability. Cortical excitability (commonly measured with transcranial magnetic stimulation [TMS]) is increased in schizophrenia, most likely due to a deficit in GABAergic neurotransmission (Hoffmann and Cavus, 2002; Daskalakis et al., 2007). Increased excitability in sensory and association cortex is associated with hallucinations (Hoffman et al., 2003; Merabet et al., 2003). A possible link to γ oscillation abnormalities in schizophrenia is suggested by the observation that chandelier cells are involved in regulating PC excitability (Zhu et al., 2004).

One of the most well-established findings in post-mortem studies of schizophrenia is of reduced synaptic connectivity in the cerebral cortex. Selemon and Goldman-Rakic (1999) proposed that increases in neuronal density in particular regions of the cortex without cell loss (Pakkenberg, 1993) reflect decreases in the neuropil due to the loss of dendritic and axonal processes. Supporting this proposal are findings such as reduced somal size, spine density, and dendritic field size of PCs (e.g., Garey et al., 1998; Glantz and Lewis, 2000; Pierri et al., 2001; Broadbelt et al., 2002; Chana et al., 2003; Black et al., 2004; Sweet et al., 2009), reduced synaptophysin levels (Perrone-Bizzozero et al., 1996; Glantz and Lewis, 1997), and decreased expression of genes encoding synaptic proteins (Mirnics et al., 2000; Torrey et al., 2005). These studies point to region-specific reductions in synaptic connectivity in schizophrenia and provide a microstructural basis for the regional cortical volume and thickness reductions found with magnetic resonance imaging (MRI) (e.g., Shenton et al., 2001; Kuperberg et al., 2003).

To date, the preponderance of evidence for synaptic connectivity reductions comes from measures of excitatory inputs to PCs. It is not known whether inhibitory interneuron connectivity is affected as well. To our knowledge, the consequences of reduced synaptic connectivity for neurophysiological activity in schizophrenia have not been studied. Therefore, we examined the effects of three kinds of synaptic connectivity reductions: excitatory connections between PCs (recurrent excitatory connectivity), recurrent excitatory and inhibitory inputs to PCs (PC input connectivity), and connections between all cells (total connectivity).

We compared connectivity reductions to the well-studied consequences of reducing FSI output. It is likely that reduced GABA synthesis in PV interneurons in schizophrenia is one cause of γ deficits, as GABA antagonism suppresses γ (Whittington et al., 1995), and decreasing the output from PV interneurons leads to decreased γ power in local circuits (Sohal et al., 2009). In modeling studies reducing the GABA output from FSIs to PCs decreased γ power (Traub et al., 2000; Vierling-Claassen et al., 2008).

Finally, a growing body of evidence links the hypofunction of *N*-methyl-D aspartate (NMDA) receptors in schizophrenia to PV interneuron abnormalities (e.g., Woo et al., 2004; Behrens et al., 2007). NMDA receptor hypofunction has been proposed to be a core neural substrate of schizophrenia (Javitt and Zukin, 1991), as NMDA receptor antagonists elicit a profile of positive and negative symptoms and cognitive deficits in healthy individuals that bears a strong resemblance to schizophrenia (Krystal et al., 2003). Studies in animal models have found that γ power (Pinault, 2008) and network activity (Homayoun and Moghaddam, 2007) can be increased by NMDA receptor antagonism, presumably by reducing the excitatory drive to PV interneurons. Therefore, we simulated the antagonism of NMDA receptors on FSIs.

MATERIALS AND METHODS

NETWORK ARCHITECTURE

The model network was implemented in the IDL programming environment (ITT Visual Information Solutions, Boulder, CO, USA) and the code is available upon request. The network consisted of 1000 leaky integrate-and-fire neurons (Burkitt, 2006), and was similar in design and behavior to other models of γ oscillations (e.g., Brunel and Wang, 2003; Borgers and Kopell, 2005). Eighty percent (800) of the cells were PCs and 20% (200) were inhibitory interneurons. Of the latter, 75% (150) were regular-spiking interneurons (RSIs) and 25% (50) were FSIs (Condé et al., 1994; Gabbott and Bacon, 1996). The FSIs and RSIs were designed to emulate the firing behavior and connectivity of PV-expressing, perisomatic-targeting interneurons (basket and chandelier cells) and apical dendrite-targeting interneurons, respectively (Zaitsev et al., 2005). Cell parameters were: resting potential: −70 mV; firing threshold: −52 mV; after-spike reset potential: −59 mV; and membrane time constant: 20 ms for PCs and RSIs, 10 ms for FSIs.

Connectivity was random. Connection probabilities were based upon the data of Gibson et al. (1999) (see **Table 1**). PCs were sparsely interconnected, while inhibitory interneurons made denser connections between themselves and PCs (particularly FSIs; Cobb et al., 1995). Synaptic weights between PCs and FSIs were stronger than other weights to simulate the faster and stronger excitation of PV interneurons than PCs (e.g., Povysheva et al., 2006), and the faster and stronger recurrent inhibition of PCs by PV interneurons than dendrite-targeting interneurons (e.g., Pouille and Scanziani, 2004; Brill and Huguenard, 2009). The spike transmission time was fixed at 2 ms.

Three synapses were modeled using differences-of-exponentials: fast excitatory [α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)], slow excitatory (NMDA), and fast inhibitory ($GABA_A$). The rise/decay time constants were: AMPA, 0.5/2 ms; NMDA, 2/100 ms; $GABA_A$, 0.5/5 ms (Brunel and Wang, 2003). The voltage dependence of the NMDA current was modeled using Equation 5 of Jahr and Stevens (1990) (1 mM Mg+ concentration). The NMDA/AMPA receptor conductance strength ratio was 45% for PCs (Myme et al., 2003). For interneurons the NMDA/AMPA ratio was set to 10% as the evidence suggests that NMDA receptors on FSIs are sparse (e.g., Muñoz et al., 1999) and contribute very little excitation (e.g., Gonzalez-Burgos et al., 2005).

Table 1 | Probability/relative weight of each connection type in the model. The relative weight of the noise input to each cell was 2. Each weight was scaled by a factor of 0.825×10^{-3} mS.

	Receiving cell		
	PC	**RSI**	**FSI**
SENDING CELL			
PC	0.10/1.0	0.40/0.8	0.40/1.9
RSI	0.50/0.8	0.15/0.8	0.50/0.8
FSI	0.50/1.9	0.35/1.0	0.60/1.0

Each cell received a separate random spike input with a frequency of 100 Hz (Poisson distribution). Noise spikes only occurred at excitatory synapses. The noise input weight was set at 16 mS. Integration was performed with the Euler method using a 0.001 ms time step (Hansel et al., 1998).

SIMULATIONS

In the connectivity experiments, connections were deleted at random from the network from 10–100% in steps of 10%. In the recurrent excitatory connectivity experiment, the excitatory connections between PCs were subject to deletion. In the PC input connectivity experiment, both excitatory connections between PCs and inhibitory inputs to PCs were deleted. In the total connectivity experiment, all connections between all cells were deleted.

In the FSI output experiment, the synaptic weights from FSIs to PCs, RSIs, and FSIs were reduced from 10–100% (steps of 10%). And in the FSI NMDA input experiment, the NMDA input to FSIs was decreased from 10–100% (steps of 10%).

For each condition of the experiments the network was initialized with the same random number generator seed so that the weight matrix and noise input were replicated. Thus, the baseline state in each experiment was the same. Additional complete sets of experiments were run with different initial conditions and the same general patterns of results were found.

ANALYSIS METHODS

Our measures were: (1) the power of the network oscillation (2) the phase synchrony between cell populations during the oscillation, and (3) the excitability of the network. The network settled into a γ oscillation by 500 ms after the start of the run (**Figure 1**), so the 500–1000 ms period was used for analysis.

To compute oscillation power, for each cell population (PCs, RSIs, and FSIs), the membrane potential was averaged across all cells within that population. The power spectrum of the average membrane potential was then computed with a Fast Fourier Transform (FFT) (2-Hz frequency resolution). This measure reflects synchronous population activity because non-synchronous activity is averaged out.

For inter-population phase synchrony, the FFT was computed on the membrane potential for each cell and converted into a phase spectrum. The phase difference was calculated for each pair of cells in comparisons between the populations (i.e., PC-RSI, PC-FSI, and RSI-FSI), and phase synchrony was computed as 1 minus the circular variance of phases (Fisher, 1993) for each between-population comparison. This measure yielded an inter-population phase synchrony spectrum which ranged from 0 (random phase distribution) to 1 (perfect phase synchrony) (cf. Lachaux et al., 1999).

Excitability was measured as simply the number of spikes during the analysis window, averaged across all the cells for each population.

RESULTS

BASELINE "HEALTHY" ACTIVITY

In the baseline condition the cells in the network generated a synchronous oscillation at 40 Hz (**Figures 1 and 2**). PC spiking was sparse, with ~5% of PCs firing on each cycle of the γ oscillation. RSI spiking was less sparse, with 12–25% of the cells spiking per γ cycle, and FSIs spiked the most, with 20–50% of the cells spiking per cycle (**Figure 2B**). The baseline spike count values were: PCs: 14.0, RSIs: 32.1, and FSIs: 58.9 spikes/cell in the analysis window.

Oscillation power was strongest for FSIs (0.819 mV^2), followed by RSIs (0.157 mV^2) and PCs (0.177 mV^2) (**Figure 3A**). As can be seen in the phase synchrony spectra (**Figure 3A**), the cell populations were closely synchronized with each other. The baseline phase synchrony values were: PC-RSI: 0.924, PC-FSI: 0.950, and RSI-FSI: 0.958.

RECURRENT EXCITATORY CONNECTIVITY

Reducing the number of connections between PCs had a dramatic effect on the network γ oscillation (**Figures 3A,B**). Power and inter-population phase synchrony were sharply reduced by the 20% level of connectivity reduction. Past the 50% level, a dominant frequency was no longer present, and the network no longer generated a coherent population oscillation.

In the excitability data (**Figure 3C**) it can be seen that the spike count for each cell population declined as recurrent excitatory connectivity was reduced. This drop-off was steepest for FSIs, which received proportionally much more excitation from PCs versus

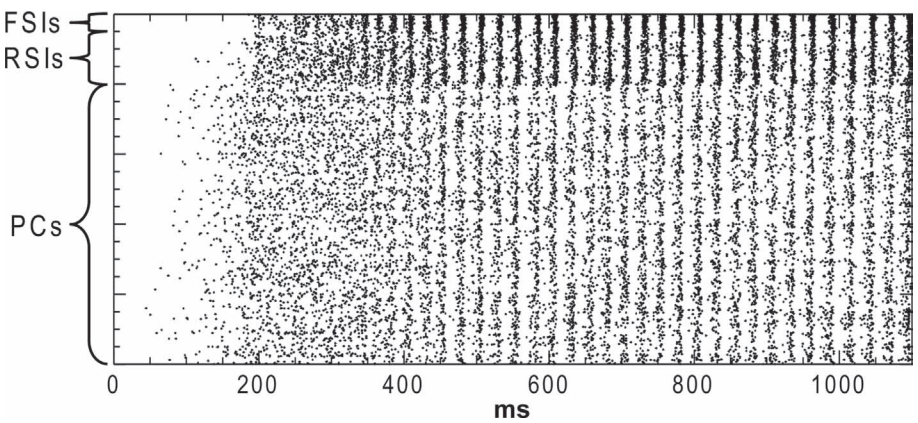

FIGURE 1 | Rastor plot of network spiking in the baseline condition. Pyramidal cells (PCs), regular-spiking interneurons (RSIs), and fast-spiking interneurons (FSIs) are indicated.

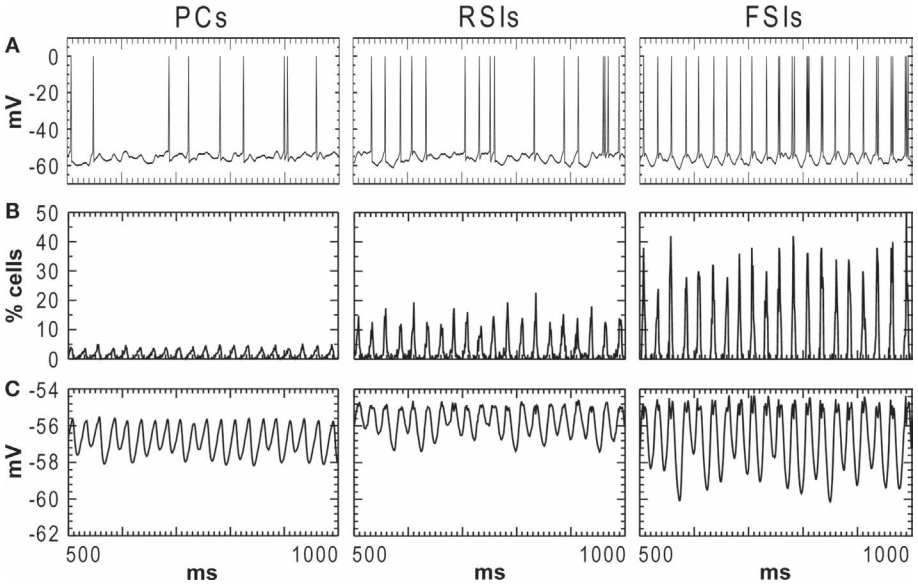

FIGURE 2 | Activity of each cell population in the baseline condition during the 500–1000 ms analysis window. (A) Individual cell membrane potentials with spikes superimposed. **(B)** Population spiking activity for each cell type, in % of cells per population (bin width = 1 ms). **(C)** Membrane potential averaged across each cell population.

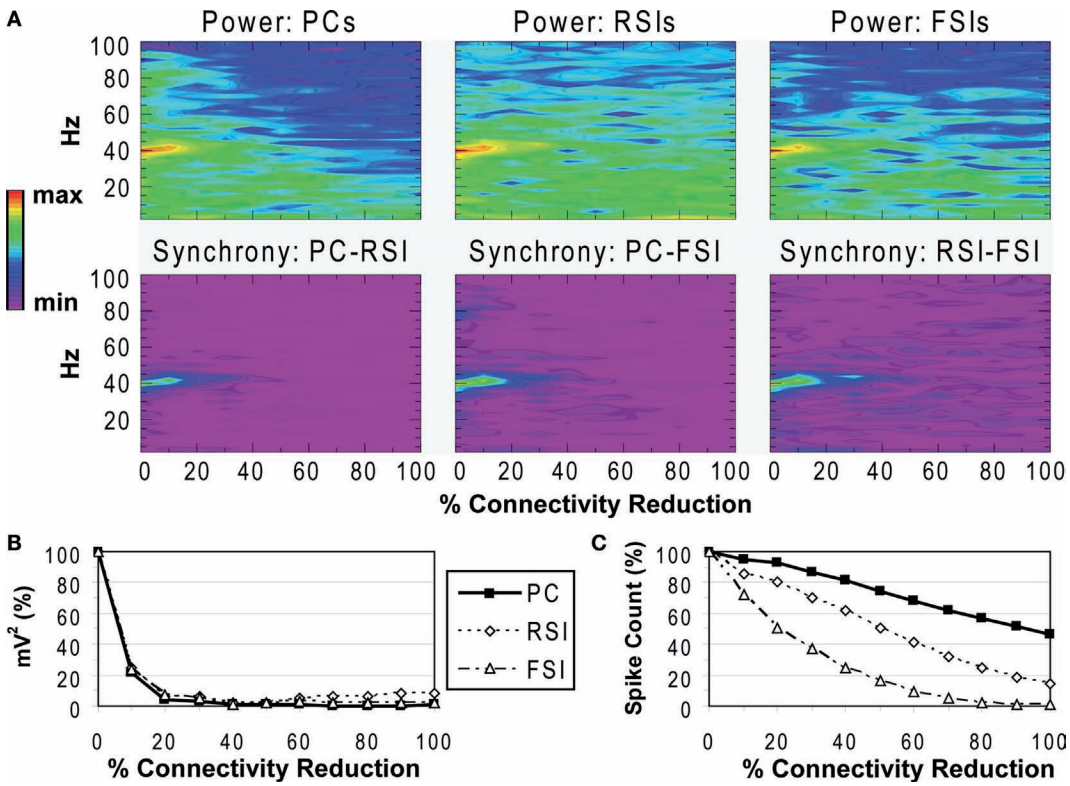

FIGURE 3 | Recurrent excitatory connectivity experiment. Measures are given as a function of % connectivity reduction. **(A)** Power and phase synchrony spectra in the γ oscillation simulation. Power (mV^2, log_{10} transformed) is scaled between the minimum and maximum for each plot. Phase synchrony is scaled from 0 to 1. **(B)** Change in peak oscillation power (mV^2) expressed as percentage of baseline. **(C)** Excitability of each cell population measured as the mean spike count, expressed as percentage of baseline.

the noise drive than PCs and RSIs, due to the stronger weights of the PC- > FSI connections (see **Table 1**). At the 20% level the FSI spike count was reduced by 50%, and approached the asymptotic value of 0 by the 70% level. PC and RSI spike counts declined to 46.3 and 14.0%, respectively, at the 100% level.

Thus, reducing PC recurrent excitation led to a decreased excitatory drive not only to the PCs but to the interneurons as well. This decrease in excitation abolished the γ oscillation and reduced network excitability.

PC INPUT CONNECTIVITY

Reducing the number of excitatory and inhibitory inputs to PCs also had a potent effect on the γ oscillation. The power and phase synchrony of the network oscillation dropped off sharply from the 0% to the 20% connectivity reduction level (**Figures 4A,B**). Past the 40% level the network ceased its synchronized oscillation.

In contrast, the effects on excitability of the cell populations (**Figure 4C**) were milder than in the recurrent excitatory connectivity experiment. The FSI spike count did not decline as steeply, instead showing an almost linear decrease to 0%. The PC spike count increased to 104.4% of baseline at the 20% level before declining, settling to a higher count than in the previous experiment (54.3% at the 100% level). The RSI spike count decreased slightly at the 10% level (98.6%) before returning to baseline at the 20% level (100.3%), and then declining to 21.6% at the 100% level.

As in the recurrent excitatory connectivity experiment, a small reduction in the number of recurrent excitatory and inhibitory inputs to PCs was sufficient to produce a robust deficit in the γ oscillation. Since phasic inhibition from interneurons to PCs is necessary for γ generation, the impairment of γ in this experiment was expected. In contrast, the concurrent loss of excitatory and inhibitory inputs to the PCs led to a different pattern in the excitability data. The loss of inhibitory inputs to the PCs counteracted the loss of excitatory inputs, and in fact led to a small disinhibitory effect in the 10–30% range of connectivity reduction. Thus, the loss of inhibitory as well as recurrent excitatory inputs to PCs partially alleviated the reduction of excitability in the network. (We note that a similar but weaker disinhibitory effect was probably present in the recurrent excitatory connectivity experiment, since a reduction in interneuron excitation would have decreased the inhibitory inputs to PCs.)

TOTAL CONNECTIVITY

Reducing the total number of connections in the network again produced a strong reduction in power and inter-population phase synchrony by the 20% connectivity reduction level (**Figures 5A,B**), although the drop-off was not as steep as in the other two experiments. The network lost coherence past the 40% level. At the 70% level the network re-synchronized in a 2 Hz oscillation that was driven by RSI-FSI synchronization, but this oscillation was not maintained at higher levels of connectivity reduction.

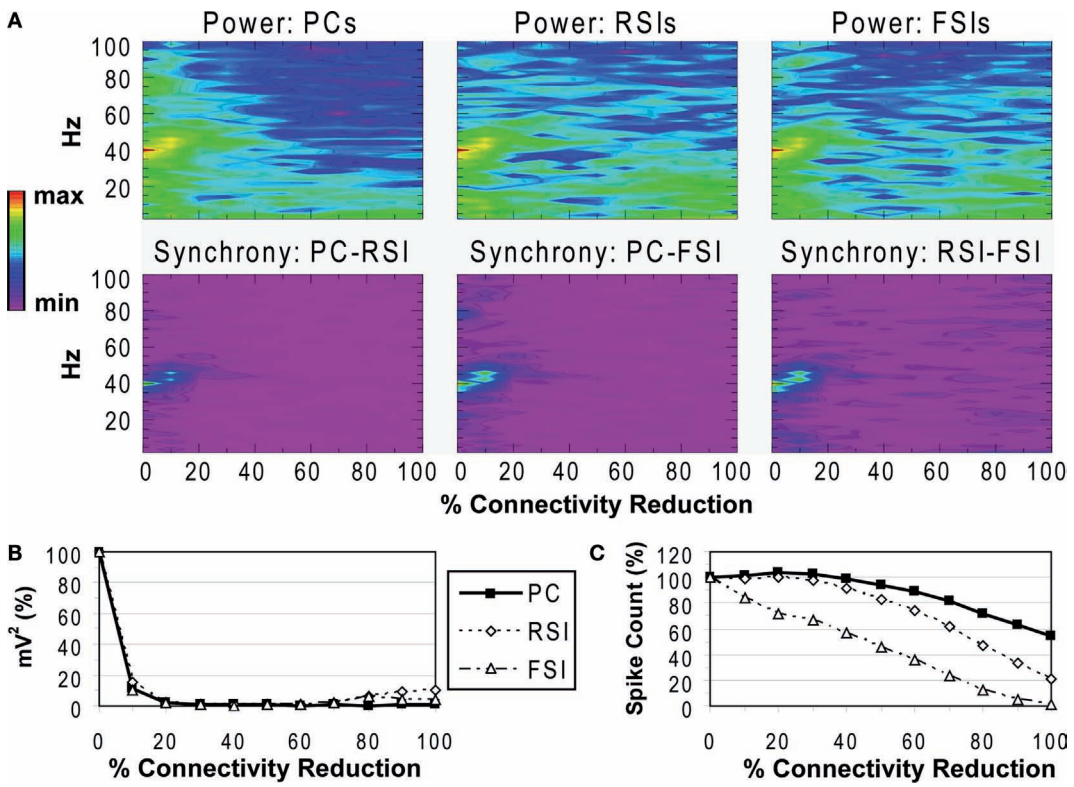

FIGURE 4 | PC input connectivity experiment. See **Figure 3** for details.

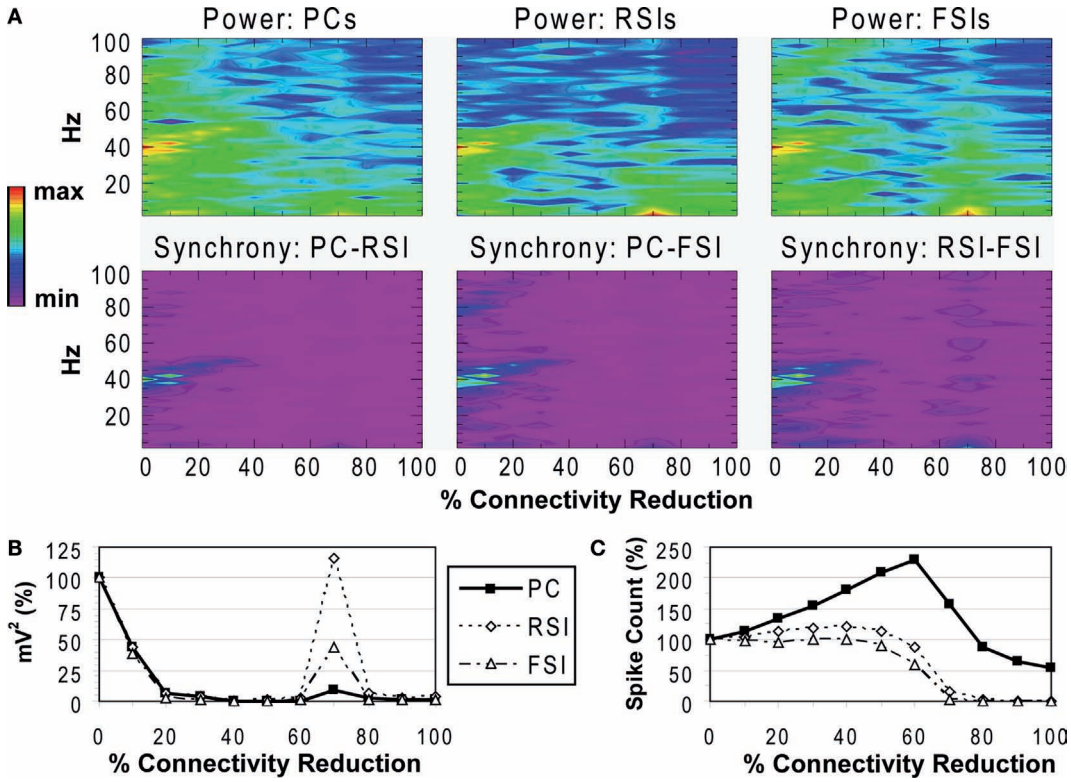

FIGURE 5 | Total connectivity experiment. See **Figure 3** for details.

The excitability data (**Figure 5C**) show that the PC spike count increased linearly from the 0% to the 60% connectivity reduction level, reaching 228% before declining to 54% at the 100% level. Between the 0% and 50% levels the RSI spike count increased from baseline, peaking at 120% at the 40% level before declining to ~0% at the 80% level. The FSI spike count stayed close to baseline from the 0% to the 50% levels before declining to 0% at the 80% level. (The preservation of PC spiking but not interneuron spiking from noise inputs at the 100% level was due to the larger NMDA/AMPA ratio in PCs.)

As in the other connectivity experiments, the γ oscillation was nearly abolished with small levels of connectivity reduction. Similar to the PC connectivity experiment, at lower levels of connectivity reduction (<60%), the loss of inhibitory connections in the network had stronger effects on excitability than the loss of excitatory connections. The loss of inhibitory connections led to an overall disinhibition that caused a large increase in PC spiking and balanced the loss of excitation in the interneurons. The disinhibitory effects were larger in this experiment because inhibitory connections between interneurons were eliminated, in addition to inhibitory inputs to PCs.

FSI OUTPUT

Reducing the weights of the connections from FSIs to other cells resulted in a different pattern of effects on network activity compared to reducing synaptic connectivity. As FSI inhibition decreased, the power and phase synchrony of the γ oscillation decreased also (**Figures 6A,B**), but to a lesser degree than in the connectivity experiments. Inter-population phase synchrony did not decrease to a large degree (under 0.5) until the 80% level of FSI output reduction. The oscillation persisted to a small degree past this level, likely mediated by the RSIs and by the high PC spike count (see below).

As FSI output decreased the excitability of all the cell populations increased due to disinhibition (**Figure 6C**). The PC spike count reached 238% and interneuron spike counts reaching ~500% at the 100% connectivity reduction level.

These results show confirm the important role that FSIs play in both network γ synchronization and in controlling cortical excitability.

FSI NMDA INPUT

Reducing the NMDA input to FSIs led to an initial decrease in γ power at the 10% level, followed by increased power from the 20–100% levels for FSIs and from the 30–80% levels for PCs and RSIs (**Figures 7A,B**). At 90–100%, γ power decreased, returning to baseline for PCs and decreasing to ~50% of baseline for RSIs. Phase synchrony of the γ oscillation showed little change, varying within a range of +/−0.05 and not dropping below 0.84 (for PC-RSI synchrony). These effects were accompanied by increased excitability for PCs and RSIs, and a slight decrease in excitability for FSIs (**Figure 7C**).

Thus, reducing the NMDA input to FSIs paradoxically resulted in a general increase in γ power and network excitability. The NMDA portion of the total excitatory input to FSIs was small,

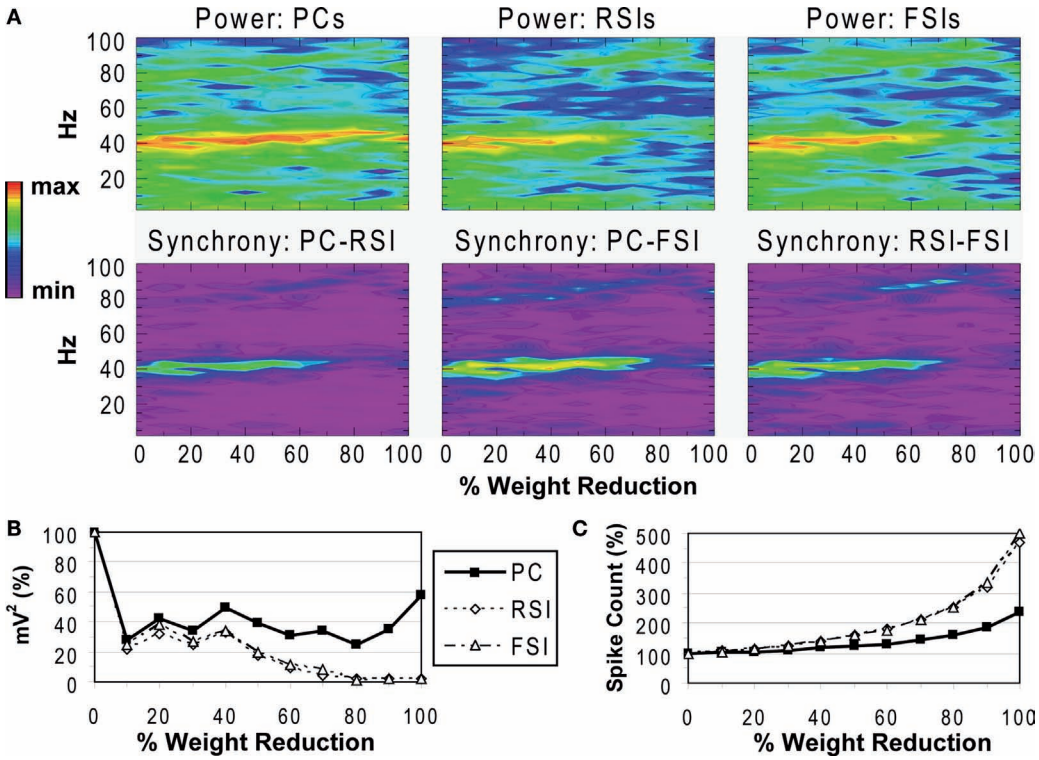

FIGURE 6 | FSI output experiment. See **Figure 3** for details.

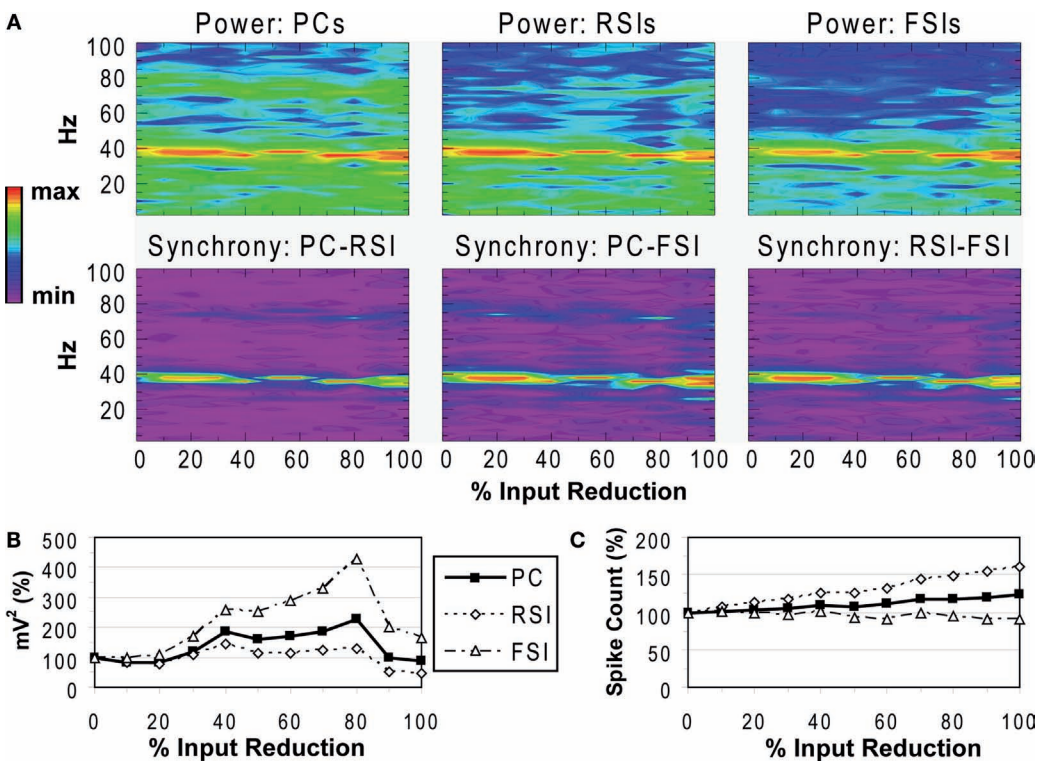

FIGURE 7 | FSI NMDA input experiment. See **Figure 3** for details.

being 10% of the AMPA contribution. Reducing the NMDA input decreased an approximately tonic source of excitation to FSIs, initially causing a drop in γ power but then resulting in increased power and PC excitability via disinhibition. In fact, removal of the tonic component of the excitatory drive to FSIs may have improved the ability of these cells to synchronize, keeping network phase synchrony from changing significantly.

DISCUSSION

SUMMARY

We examined the effects of reductions in synaptic connectivity, FSI output, and NMDA input to FSIs on γ generation and excitability in a model cortical network. Generally, small reductions of synaptic connectivity (10–20%) produced large decreases in the power and inter-population phase synchrony of the γ oscillation, regardless of the kind of connections that were affected. In contrast, the kind of connectivity reduction influenced the patterns of cell excitability: deleting only recurrent excitatory connections decreased the excitability of all three cell populations, while additionally deleting inhibitory connections resulted in increased excitability due to disinhibition at lower levels of connectivity reduction. At higher levels of connectivity reduction, excitability decreased. In comparison, reducing FSI output decreased γ power and synchrony to a lesser degree, and increased network excitability through disinhibition. Reducing the NMDA input to FSIs also increased network excitability, and γ power increased while phase synchrony was relatively unaffected.

VALIDITY OF THE MODEL

Our model of cortical circuitry produced a population oscillation in the γ frequency range when driven by noise inputs at excitatory synapses. The noise input functions in roughly the same manner as a constant current input: it provides an approximately tonic excitatory drive to the cells through the NMDA receptors. As a result of this drive, a fast oscillation emerges in the network from the interplay between PCs and inhibitory interneurons. (In pilot work we found that the frequency of the oscillation depended partially on the strength of the noise input, increasing for stronger inputs above a particular threshold.) The γ oscillation produced by this kind of model resembles the oscillations seen *in vivo* in the hippocampus and neocortex (e.g., Oren et al., 2006; Roopun et al., 2008; Sohal et al., 2009).

In other pilot experiments the network could generate an "evoked" γ oscillation when given a transient, rather than tonic, stimulus. This effect resembles the EEG pattern evoked by TMS (e.g., Ferrarelli et al., 2008), and might serve as a model for TMS-EEG phenomena. When the network was given steady-state stimulation in addition to noise input, it produced a steady-state response at the stimulation frequency, with an enhancement of this response at the resonant frequency of the network (40 Hz in this case). So this seems to be a reasonable if simplified model of "real" γ rhythms.

REDUCED SYNAPTIC CONNECTIVITY

Spine density measurements offer the closest comparable data to the synaptic connectivity reductions simulated here. Spines are the principal site of glutamatergic synapses on PCs (Nimchinsky et al., 2002), but a small portion of spines also includes GABAergic synapses (~3%; Kubota et al., 2007). Therefore, spine density measurements in schizophrenia reflect predominantly excitatory inputs to PCs. Since the abnormalities that have been observed have been found mainly in layers 3 and 5, they are likely to involve primarily intracortical circuits, and thus recurrent excitation.

Deleting just recurrent excitatory connections was sufficient to abolish the network γ oscillation. This finding suggests that the excitatory drive to the network furnished by recurrent excitation was necessary for γ generation. However, the additional deletion of inhibitory connections increased PC spiking via disinhibition while reducing the γ oscillation to a similar degree. Thus, the impairment of γ generation by reduced synaptic connectivity was not tied to the specific type of connection deleted. Rather, it reflected the altered structure of the network. This result is consistent with findings from other modeling studies that a minimum number of connections is necessary for γ synchronization (e.g., Wang and Buzsaki, 1996; Borgers and Kopell, 2003), although the precise number varies due to differences in the models.

Another potential factor that could result in a reduction of the power of the network oscillation is an increase in the variance of the number of inputs per cell (Borgers and Kopell, 2003). We investigated this possibility, but the variance in inputs per cell decreased as connectivity was reduced, so the disruption of γ synchronization was not caused by increased input variance.

PC spine density in post-mortem samples has been studied in several brain areas, and significant reductions in schizophrenia patients have ranged from 15% to 55% (Garey et al., 1998; Glantz and Lewis, 2000; Broadbelt et al., 2002; Sweet et al., 2009). In all of our synaptic connectivity experiments this range of reduction was sufficient to produce a large deficit in γ. Thus, a γ deficit in schizophrenia patients could be a marker of reduced synaptic connectivity in the underlying cortical network. However, it is unknown to what extent inhibitory connectivity might also be affected in schizophrenia. Our simulations suggest that a γ deficit would not be indicative of the type of the underlying synaptic connectivity abnormality.

The degree to which cortical volume/thickness reductions in schizophrenia reflect synaptic connectivity reductions at the circuit level is not presently known. Regional reductions of cortical volume range up to 15% at the group level (Shenton et al., 2001). The present data suggest that γ may be a more sensitive indicator of circuit integrity than MRI measures, as only a 10% decrease in synaptic connectivity was sufficient to produce a sizable γ deficit.

REDUCED FSI OUTPUT

In post-mortem schizophrenia samples, the expression of GAD67, an enzyme required for GABA synthesis, has been reported to be reduced to undetectable levels in PV-expressing interneurons (e.g., Hashimoto et al., 2003). Hence, the upper levels of FSI output reduction in our model are probably the most relevant. At these levels γ generation was impaired, although not as severely as when synaptic connectivity was reduced. Sohal et al. (2009) used optogenetic techniques to inhibit the firing of PV-expressing interneurons *in vivo* and also found a modest reduction of γ. These relatively smaller impairments could be due to the participation of other

interneuron classes in the γ oscillation (e.g., Oren et al., 2006). The increase in network excitability due to FSI output reduction was consistent with experimental evidence (Zhu et al., 2004).

REDUCED NMDA INPUT TO FSIs

Reduced NMDA input to FSIs produced a clear signature: an increase in γ power, along with increased network excitability. These effects are consistent with those of NMDA receptor antagonism reported respectively by Pinault (2008) and Homayoun and Moghaddam (2007). These findings suggest that the administration of NMDA receptor antagonists at subanesthetic doses preferentially affects NMDA receptors on PV interneurons. However, it should be noted that this effect is regionally specific, as γ increases and decreases due to NMDA receptor antagonism have been reported in various brain regions (Roopun et al., 2008). Modeling may prove useful in understanding the basis of these regional variations.

IMPLICATIONS

The main goal of this study was to determine if different kinds of neural circuitry abnormalities associated with schizophrenia – synaptic connectivity reductions, reduced FSI output, and reduced NMDA input to FSIs – would produce distinct patterns of effects that might be make them detectable with non-invasive measures such as EEG and MRI. We found that reductions of synaptic connectivity and FSI output produced γ deficits, while reduced NMDA input to FSIs produced γ increases. Network excitability changes demonstrated a different pattern: excitability decreased when recurrent excitation was reduced, while excitability increased when the FSI contribution to network activity was reduced, either by deleting inhibitory inputs to PCs, reducing FSI outputs, or decreasing the NMDA-mediated depolarization of FSIs. Therefore, the identification of microcircuit abnormalities in schizophrenia patients with non-invasive methods is likely to require a multimodal approach that combines neurophysiological and neuroanatomical methodologies.

Most reports to date of γ oscillation abnormalities in schizophrenia have found that the power and/or phase synchronization of γ oscillations are reduced in schizophrenia patients relative to healthy individuals (see Introduction). Here we found that γ deficits could be ascribed to both synaptic connectivity and FSI output reductions. In principle, these causes could be distinguished by localizing the neuroanatomical source of an oscillation, then measuring the volume and/or thickness of the generating cortical region with MRI techniques. A γ deficit with normal structural measurements of the generating cortex would point to a deficit in GABAergic transmission, whereas a γ deficit with reduced cortical volume would suggest reduced synaptic connectivity as a cause (not excluding the possibility of a GABAergic deficit).

TMS would add a complementary dimension to this approach. By measuring the excitability of the generating region of a γ oscillation it would be possible to determine whether a deficit in inhibitory function was present. TMS would be sensitive to reduced FSI output, reduced NMDA input to FSIs, and presumably reduced inhibitory connectivity, as all three of these abnormalities lead to increased network excitability. If structural MRI analysis found evidence of reduced synaptic connectivity in the region, normal excitability measures would indicate that this abnormality involved only recurrent excitation. On the other hand, if increased excitability was present, this would indicate that inhibitory function was also affected. Standard cortical excitability measurements with TMS are limited by the necessity of having an output measure such as motor evoked potentials, which are not available in most cortical areas, but TMS-evoked EEG oscillations may provide a new tool with which to assess circuit integrity (e.g., Ferrarelli et al., 2008).

Not all γ abnormalities in schizophrenia are deficits. A few studies have reported that across patients, the power and/or phase synchronization of certain γ/β oscillations are positively correlated with symptom measures (Spencer et al., 2004, 2008b, 2009). It is noteworthy that these positive correlations have been found mainly for psychotic symptoms, especially hallucinations. These findings imply that psychosis may be associated in some circumstances with an excessive degree of oscillatory synchronization. Since the only known circuit abnormality in schizophrenia that can produce increased γ power is NMDA receptor hypofunction, positive correlations between γ/β oscillations and psychotic symptoms may reflect dysfunctional NMDA input to FSIs. This hypothesis, however, is complicated by the co-occurrence of positive correlations within patient groups with overall γ deficits at the group level (Spencer et al., 2008b, 2009).

For instance, Spencer et al. (2009) found that the phase locking aspect of the 40 Hz auditory steady-state response (ASSR) in the left auditory cortex of schizophrenia patients was decreased relative to control subjects. Within the patient group, though, there was a positive correlation between auditory hallucination symptom scores and phase locking, such that the most symptomatic patients had nearly normal phase locking values. This pattern suggests the presence of multiple neural circuitry abnormalities within the generating region, and a multimodal imaging approach would be necessary to identify these abnormalities. Combining EEG source localization with structural MRI, we would predict that the overall ASSR deficit in patients would be accounted for by a reduction of primary auditory cortex volume (the main ASSR generator; e.g., Hirayasu et al., 2000), while NMDA receptor hypofunction in patients with hallucinations would explain the positive γ/hallucination correlation.

While we did not attempt to simulate the blood oxygenation level-dependent (BOLD) response here, a number of studies have found that the BOLD response measured with functional MRI is correlated with local field potentials in the γ band (e.g., Logothetis et al., 2001; Niessing et al., 2005), as well as intracranial (Mukamel et al., 2005; Lachaux et al., 2007) and non-invasive recordings of γ oscillations in humans (e.g., Brookes et al., 2005; Martuzzi et al., 2009; Zaehle et al., 2009; but see Winterer et al., 2007; Muthukumaraswamy and Singh, 2009; Muthukumaraswamy et al., 2009). Thus, it might be reasonable to predict that microcircuit abnormalities that cause decreases or increases in γ power would produce similar changes in the BOLD response. This relationship should be particularly expected for synaptic connectivity reductions, since it is thought that the BOLD response mainly reflects the metabolic demand of the synaptic input to a cortical area, rather than its spiking output (e.g., Viswanathan and Freeman,

2007). With reduced synaptic connectivity in a cortical area there would be fewer synaptic inputs, the change in metabolism in response to changing inputs would be reduced, and the BOLD response would thus be decreased.

In contrast, since NMDA receptor antagonism increases neural activity through disinhibition (Homayoun and Moghaddam, 2007), the BOLD response would be expected to increase for circuits affected by reduced NMDA input to FSIs. Studies of non-schizophrenic visual hallucinators have reported increased baseline activity as measured by BOLD (ffytche et al., 1998) and increased excitability as measured by TMS (Merabet et al., 2003) in visual cortex, which would both be consistent with NMDA receptor hypofunction.

It is not as clear what effects reduced FSI output due to reduced GABA synthesis would have on the BOLD response. A moderate reduction might be expected, given that there was a moderate reduction in γ power. However, Muthukumaraswamy et al. (2009) found that the BOLD response to visual stimulation in primary visual cortex was negatively correlated with the concentration of GABA in the same area, as measured by magnetic resonance spectroscopy, so that as GABA concentration increased, the BOLD response decreased. The power of a γ oscillation generated in the same area of visual cortex was not correlated with the BOLD response, but the frequency of the oscillation was positively correlated with GABA concentration. As it is not presently known how resting GABA concentration is functionally related to network activity (BOLD and γ) during stimulation, more data are needed to understand how these findings might pertain to schizophrenia, but the multimodal approach these authors employed can clearly provide new insights into cortical physiology.

LIMITATIONS OF THE PRESENT STUDY AND FUTURE DIRECTIONS

This study had several limitations. While we attempted to make the connectivity parameters as close as possible to published observations, laminar connectivity was not modeled. Furthermore, the neuron dynamics were very simple (for instance, there was no spike adaptation or bursting) and were much less heterogeneous than in real cortical circuits. Also, the spike transmission time was fixed rather than variable. Nevertheless, these factors should not make our results less valid. Rather, γ synchronization might be even more susceptible to disruption by reducing connectivity in models with more complex dynamics and heterogeneous cell types (Santhakumar and Soltesz, 2004).

In future studies it will be important to examine synaptic connectivity in networks that incorporate laminar connectivity patterns, as synaptic connectivity reductions have been localized to particular layers. For instance, Sweet and colleagues have found evidence that intrinsic processing within the primary auditory cortex, and feedforward but not feedback circuits from primary to associational auditory cortex, are dysfunctional in schizophrenia (e.g., Sweet et al., 2004, 2007). We will also examine how abnormalities in the circuitry of one cortical region may affect γ synchronization and network excitability in a distant area.

We note that one major question that has not yet been examined in post-mortem studies is whether inhibitory connectivity is impaired in schizophrenia. Furthermore, it would be useful to understand the degree to which GAD67 expression correlates with the functional output of inhibitory interneurons.

CONCLUSIONS

Computational modeling may help to bridge the gaps between post-mortem studies, animal models, and experimental data in humans. The strength of this approach is that it affords the ability to completely control and measure all aspects of the system under study. By simulating the neural circuit abnormalities found in schizophrenia, it is in principle possible to study the responses of these altered neural circuits in a potentially more realistic manner than by using animal models which approximate certain aspects of the disorder.

One use of computational modeling in schizophrenia research is to test hypotheses about the functional consequences of particular neural circuit abnormalities, as was done here. Another use of computational modeling is to explore the efficacy of different drugs on various aspects of neural circuit function that would be difficult to measure collectively *in vivo*. For instance, the actions of GABA- vs. glutamate-targeting drugs could be compared on biomarkers such as γ oscillations, cortical excitability, sustained activity, and plasticity. Both types of medications are designed to improve the function of FSIs but in different ways. A GABA agonist might reduce cortical excitability but not improve working memory-related sustained activity, while an NMDA agonist might improve both biomarkers. Exploring drug effects on neural circuits via modeling could provide clues as to how these drugs might work and reveal which biomarkers might be most sensitive to their effects. In this manner, the precision of drug development might be enhanced and the discovery process facilitated.

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Convergent approaches for defining functional imaging endophenotypes in schizophrenia

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In complex genetic disorders such as schizophrenia, endophenotypes have potential utility both in identifying risk genes and in illuminating pathophysiology. This is due to their presumed status as closer in the etiopathological pathway to the causative genes than is the currently defining clinical phenomenology of the illness and thus their simpler genetic architecture than that of the full syndrome. There, many genes conferring slight individual risk are additive or epistatic (interactive) with regard to cumulative schizophrenia risk. In addition the use of endophenotypes has encouraged a conceptual shift away from the exclusive study of categorical diagnoses in manifestly ill patients, towards the study of quantitative traits in patients, unaffected relatives and healthy controls. A more recently employed strategy is thus to study unaffected first-degree relatives of schizophrenia patients, who share some of the genetic diathesis without illness-related confounds that may themselves impact fMRI task performance. Consistent with the multiple biological abnormalities associated with the disorder, many candidate endophenotypes have been advanced for schizophrenia, including measures derived from structural brain imaging, EEG, sensorimotor integration, eye movements and cognitive performance (Allen et al., 2009), but recent data derived from quantitative functional brain imaging measures present additional attractive putative endophenotypes. We will review two major, conceptually different approaches that use fMRI in this context. One, the dominant paradigm, employs defined cognitive tasks on which schizophrenia patients perform poorly as "cognitive stress tests". The second uses very simple probes or "task-free" approaches where performance in patients and controls is equal. We explore the potential advantages and disadvantages of each method, the associated data analytic approaches and recent studies exploring their interface with the genetic risk architecture of schizophrenia.

Keywords: fMRI, schizophrenia, endophenotype, intermediate phenotype, working memory, independent component analysis, default mode, resting state

WHY ARE ENDOPHENOTYPES IMPORTANT? DEFINITIONS OF ENDOPHENOTYPES VERSUS BIOMARKERS AND MAJOR IMPLICATIONS

Schizophrenia is an inherited, complex genetic disorder currently defined categorically on the basis of cross-sectional symptoms and longitudinal course, but not underpinned by any objective biological measures or physical/neurologic signs. This is problematic as:

(a) schizophrenia is complex at the level of the phenotype, due to high variability and mutability of the defining clinical symptoms.
(b) patients may refuse to disclose their symptoms (due for example to paranoid suspiciousness, itself a common symptom of the illness), or
(c) individuals may claim falsely to have symptoms (for example in a legal context), that are by nature unverifiable and
(d) although the clinical symptomatology of schizophrenia can be striking, there are no pathognomonic symptoms, (for example considerable overlap exists between symptoms of schizophrenia and those of psychotic bipolar disorder).

Because the pathophysiology of schizophrenia is obscure, there is no laboratory test or biological marker deriving from the core etiopathology. *Biomarkers* are quantitative characteristics that signal normal or abnormal biologic processes, or predict treatment response. For particular pathologic states they are disease-specific flags of its existence or severity, directly associated with clinical manifestations and outcome (Allen et al., 2009; Ritsner and Gottesman, 2009). For example, hemoglobin A1c (or glycosylated hemoglobin) in Type II diabetes is related both to pathophysiology (altered carbohydrate metabolism) and indicates an important disease feature, (abnormally elevated blood glucose). Because the classical phenotype of schizophrenia is complex, varied and overlaps extensively with that of other illnesses such as psychotic bipolar disorder, the search for biological markers associated with schizophrenia has been a difficult one.

Because of such problems investigators in recent years have focused more on endophenotypes then on biomarkers. In contrast to biological markers, *endophenotypes* or "intermediate phenotypes," are viewed as quantifiable biological variations or deficits that are examples of stable trait markers or indicators of presumed inherited disease vulnerability (for recent reviews,

see Prasad and Keshavan, 2008; Allen et al., 2009; Ritsner and Gottesman, 2009). Endophenotypes, as conceived by Gottesman and colleagues (e.g. Gottesman and Gould, 2003; Chan and Gottesman, 2008) and elaborated by others (Pearlson and Folley, 2008a,b; Prasad and Keshavan, 2008; Allen et al., 2009), are heritable, quantitative traits associated with an illness both epidemiologically and also conceptually in the sense of being on the putative path from genes, via molecular biologic mechanisms, to brain states to overt behavior. They are state-independent (i.e. not only present during acute illness), co-segregate within families and occur in some unaffected relatives of individuals with the disorder, (because they represent vulnerability for the disorder), although at a higher prevalence than in the general population. They may not be visible to the naked eye and are generally assessed by experimental, laboratory-based methods rather than by clinical observation; this approach may include challenge tests to "unmask" the marker. Because schizophrenia is likely a common, multi-genetic disorder (analogous to hypertension or type II diabetes) endophenotype strategies are increasingly used by researchers, based on the presumption that endophenotypes are more straightforwardly inherited and are underpinned by fewer genes than are complex, heterogeneous phenomenological entities such as clinical psychiatric diagnostic categories (Pearlson and Folley, 2008a,b). Because endophenotypes are "intermediate" between a clinical syndrome and the associated disease vulnerability genes (illness markers not illness features) using them therefore simplifies the search for the etiopathology and genetic determinants of schizophrenia (Chan and Gottesman, 2008; Pearlson and Folley, 2008a,b).

The reader is referred to a recent review of schizophrenia-associated endophenotypes (Allen et al., 2009). Despite displaying some useful properties (Prasad and Keshavan, 2008), employment of structural brain imaging endophenotypes in schizophrenia has generally been limited by their low diagnostic specificity. Endophenotypes derived from functional imaging paradigms seem intuitively more promising, but there is an enormous variety of these from which to choose. This article contrasts two very different such functional endophenotypes; those associated with working memory (WM) tasks versus those related to simple or no cognitive tasks. As well as task type, analytic strategies also vary. The majority of task-related functional studies in schizophrenia are analyzed using classic general linear model (GLM) based approaches; recently, newer analytic paradigms such as independent component analysis (ICA) have opened up new possibilities for both task-related and unrelated designs.

There are problems inherent in the predominant fMRI research strategy of focusing on challenge tasks based in cognitive domains where schizophrenia patients are behaviorally impaired, such as WM. Such problems include that patients often do not fully comprehend complex instructions and have problems performing tasks consistently in the scanner. They fatigue easily, have generally reduced concentration and attention, may be poorly motivated, distracted by illness symptoms such as hallucinations and sedated from medication side effects. Poor performance and abnormal task-related BOLD response are thus confounded in a "chicken and egg" situation which may be difficult to disambiguate. One solution to this problem has been to use easy or minimal-effort paradigms such as oddball tasks in which patients and controls perform at comparable levels of accuracy, or even imaging during rest, when there is no task (such as resting state/default mode paradigms), requiring no cognitive effort on the part of the subject (e.g. Greicius et al., 2004; Bluhm et al., 2007; Garrity et al., 2007).

Some of the major contrasts between these two divergent types of studies discussed in this article are highlighted in **Table 1**, which cites representative and recent widely cited illustrative articles and reviews whose general topic headings are elaborated in detail in the remainder of the paper.

CURRENT NEUROIMAGING APPROACHES USING COGNITION; DLPFC IN PATIENTS AND IN RELATIVES

Working memory, the ability to hold information on-line and manipulate it for short periods of time (Baddeley, 1992) has been studied in depth in humans and animals. WM and related executive abilities, (e.g. planning, multi-tasking), are characteristically impaired in schizophrenia, Silver et al. (2003). Schizophrenia patients exhibit deficits on WM tasks of many designs (Park and Holzman, 1992; Cohen et al., 1996; Barch et al., 1998, 2009; Goldberg et al., 1998; Wexler et al., 1998; Park et al., 1999). Such WM performance disturbances in schizophrenia are present in never-treated, first-episode, acutely ill and chronic patients and also (to a lesser degree) in their unaffected first-degree relatives, including discordant twins (Callicott et al., 2003a; Barch and Smith, 2008; Meda et al., 2008). Issues related to WM abnormalities in schizophrenia have become methodological test-beds in the research field as the allied pathophysiology has been so well studied in this disorder and reflects daily life functioning (Green, 1996).

For these reasons, different types of WM paradigms have been chosen as the basis of dominant type of cognitive functional MRI task studied in schizophrenia patients. Following on WM studies of nonhuman primates (Friedman and Goldman-Rakic, 1994; Petrides, 1995; Miller et al., 1996), human WM fMRI studies have largely focused anatomically on the dorsolateral prefrontal cortex (DLPFC), a similarly involved area in humans (D'Esposito et al., 1999; Rypma and D'Esposito, 1999; Manoach et al., 2003; Veltman et al., 2003). DLPFC likely plays a crucial role in coordinating a distributed, executive task-relevant functional network. Additional modules in this circuit include other frontal regions, (ventrolateral and polar PFC and anterior cingulate), plus inferior parietal lobule (Manoach et al., 2003; Meda et al., 2008) and hippocampus (Glahn et al., 2005; Meda et al., 2008).

fMRI studies in schizophrenia typically center on patient/control DLPFC activation differences. Reports disagree on the direction of differences (see meta-analysis of Van Snellenberg et al., 2006), with some findings of patient DLFPC underactivation compared to controls (Yurgelun-Todd et al., 1996; Callicott et al., 1998) and others of patient overactivation (Manoach et al., 2000; Callicott et al., 2003b). Evidence suggests that the magnitude and direction of BOLD response vary depending on relative task difficulty in relation to a given individual's baseline efficiency on a particular task, (Manoach et al., 2000; Callicott et al., 2003b; Johnson et al., 2006; Meda et al., 2008). Thus, under conditions of equivalent task performance, schizophrenia patients activate DLPFC "inefficiently," manifesting more WM-related activation than controls (Callicott et al., 1999, 2003b). With increasing task difficulty, patients exceed

Table 1 | Comparison of endophenotypic properties of working memory and default mode/resting state studies in schizophrenia and controls.

	fMRI working memory paradigms	fMRI resting state and default modes
Associated with illness	Meyer-Lindenberg and Weinberger, 2006; Glahn et al., under review; Ragland et al., 2007	Garrity et al., 2007; Jafri et al., 2008: Broyd et al., 2009
State independent	Ragland et al., 2007	Broyd et al., 2009
Heritable	Blokland et al., 2008**	Glahn*
Present in unaffected family members	Callicott et al., 2003a; Winterer et al., 2004; Meda et al., 2008	Whitfield-Gabrieli et al., 2009
May be related to "cause" ("disconnection", DLPFC inefficiency, etc)	Winterer et al., 2004; Meyer-Lindenberg and Weinberger, 2006	Calhoun et al., in press
Quantitative, measured reliably	Ragland et al., 2007	Broyd et al., 2009; Calhoun et al., in press
Stability over time (test-retest)		Broyd et al., 2009
Diagnostic specificity		Calhoun et al., 2008b *(Schizophrenia vs bipolar)*
Partially identified genetic basis	Meyer-Lindenberg and Weinberger, 2006	Meda et al., under review
"Good candidate endophenotype"	Allen et al., 2009	Meyer-Lindenberg, 2009

**D. Glahn et al., under review based on preliminary data in 333 subjects from the San Antonio study.*

***h^2 (heritability) was not significant, but heritability values were higher in monozygotic than dizygotic twins.*

their cognitive capacity, leading to their disengaging or performing poorly, with consequent relative DLPFC underactivation (Callicott et al., 2000, 2003b; Manoach et al., 2000; Manoach 2003; Johnson et al., 2006). Thus, WM load correlates with DLPFC activation in an inverted U-shaped curve; the curve in schizophrenia is both be flatter and shifted towards the left compared to controls, reflecting their inefficient task-related BOLD- response (Callicott et al., 2003b; Johnson, et al., 2006). Schizophrenia may also be associated with reduced ability to use context to guide task performance (Cohen et al., 1996; Servan-Schreiber et al., 1996; Barch et al., 2001; Henik et al., 2002; Ford et al., 2004; Johnson et al., 2006).

Different WM investigations in schizophrenia have utilized different task designs to best highlight particular aspects of abnormal responding in patients. Load vs BOLD response effects are most often demonstrated by measuring activation at several levels of increasing memory load, often by using N-back WM tasks (e.g. Callicott et al., 1999, 2000; Perlstein et al., 2001; Jansma et al., 2004). N-back designs however have unavoidable design problems. Usually, they incorporate target stimuli as probes, conflating the separate WM subprocesses of encoding, maintenance, and retrieval. Ideally, these are modeled separately, as their underlying functional anatomy may differ. Also in schizophrenia, the different subprocesses may be differentially impaired. Second, the steep difficulty gradient of the task curtails WM load-related response to three WM difficulty levels. Related to this, the 1-back level is generally easy for both control and schizophrenia subjects, but the 3-back condition exceeds WM capacity in many patients and some healthy controls. Patients, aware of their poorer task performance at more difficult levels, can become demoralized, unmotivated and disengaged from the task.

For the above reasons, some investigators have preferred to use versions of the Sternberg Item Recognition Paradigm (Sternberg, 1966) to examine WM (Manoach et al., 1997, 2000, 2003; Veltman et al., 2003; Johnson et al., 2006; Meda et al., 2008) because WM load can be increased more gradually and the distinct task stages separated more easily; relative to the N-Back task, the Sternberg task allows a clearer temporal dissociation of encoding, maintenance, and response selection/response selection phases of WM.

Despite the numerous WM studies in the schizophrenia literature, and the demonstration of abnormal cortical connectivity (Meyer-Lindenberg et al., 2001), several important questions remain to be clarified regarding the specific neural underpinning of impaired cognition in schizophrenia. For example, task-related DLPFC activation in schizophrenia is often more diffuse, less restricted to DLPFC and more likely to involve anteromedial and ventral frontal activation., This phenomenon is not related to the specific WM task employed, but could represent a result of DLPFC inefficiency, resulting in the need for backup recruitment of neighboring regions (e.g. as argued by Glahn et al., 2005; Ragland et al., 2007). In addition, the epicenter of DLPFC activation in schizophrenia differs from that identified in controls, being located in regions close by (Glahn et al., 2005). This phenomenon could either be based on abnormal functional connectivity, or on deviant structurally-based functional localization e.g. see MacDonald et al. (2006). While a more recent quantitative meta-analysis (Minzenberg et al., 2009) discusses aspects of this issue, the more over arching question has to do with the fundamental underlying mechanisms. Until these are better clarified for example in the biochemical or genetic level

the resulting phenomena (i.e. reduced motivation etc.) introduce design issues that cloud the ability to integrate fully across levels of measurement.

With regard to identifying the precise nature and progression of WM abnormalities in schizophrenia (and unaffected relatives), one debate centers on the specificity of WM deficits to task phase (e.g. MacDonald et al., 2003). Future studies will likely focus more on modeling the maintenance period between encoding and retrieval, which has been relatively understudied, but may be crucial. For example, Driesen et al. (2008) showed reduced prefrontal activity in patients during the maintenance phase, related to a faster decay rate of activity over time.

In summary, abnormal WM-related fMRI activation in occurs in a network, not just a single region (the DLPFC). The network in schizophrenia patients performs less efficiently, is less context-responsive to and does not react smoothly to changing load demands; the maintenance period may be especially impaired. Both hyper- and hypo-activation in patients are explainable by an inability to efficiently organize and distribute appropriate circuit resources as needed for effective WM performance.

Abnormal WM-based fMRI BOLD response was chosen as a potential schizophrenia endophenotype based on findings of WM performance deficits in non-affected siblings of schizophrenia patients and in discordant twin studies (Park et al., 1995; Goldberg et al., 2003; MacDonald et al., 2003). As predicted, in fMRI studies, unaffected siblings also show aberrant DLPFC activation during WM tasks, even in some cases in the face of normal task performance, emphasizing the point made earlier that the endophenotype may be closer to the pathologic mechanism than to overt behavior. For example Callicott et al. (2003a) found increased DLPFC activation in unaffected sibs of patients versus controls during encoding and manipulation of information, despite normal task performance. Brahmbhatt et al. (2006) determined that high-risk siblings abnormally hyperactivated PFC during response selection. Thermenos et al. (2004), using a combined attention/WM task, showed unaffected relatives had more task-related activation in prefrontal cortex and thalamus; when task performance was controlled, relatives over-activated. Finally, Meda et al. (2008) in an fMRI Sternberg WM task, reported that performance accuracy in unaffected first-degree relatives did not differ from controls (although relatives were slower in responding to probes). The major functional differences were that relatives hypo-activated bilateral dorsolateral/ventrolateral prefrontal cortices (DLPFC/VLPFC) and the posterior parietal cortex during stimulus encoding epochs and hypo-activated bilateral DLPFC and parietal areas during response selection. fMRI differences in both conditions were load-modulated, with a parametric increase in between-group differences with load in key regions during encoding and an opposite effect during response selection. While Callicott et al. (2003a) and Thermenos et al. (2004), reported increased DLPFC activation, Meda found DLPFC underactivation in both encoding and response selection task phases, likely related to differences in task design or difficulty, as discussed earlier. Thus in sum, (as reviewed by Meyer-Lindenberg and Weinberger, 2006), abnormal WM fMRI responses in unaffected relatives in addition to those in patients confirmed their suitability as potential endophenotype candidates.

A richer explanatory context is now emerging for the abnormal fMRI WM findings in schizophrenia. As we mentioned above, an earlier, simpler approach was to view schizophrenia as a primary DLPFC defect, with resulting WM deficits underlying both other cognitive deficits and major positive symptoms of the disorder (e.g. see Cohen et al., 1996; Silver et al., 2003) However, cognitive neuroscience suggests that network-level abnormalities at the level of circuits can better account for the WM abnormalities in schizophrenia than explanations based on a single region, in a manner that also has interesting implications consistent with the concept of schizophrenia as a "disconnection syndrome" (Friston and Frith, 1995). Evidence for this hypothesis is emerging from ICA, a data-driven approach especially useful for decomposing activation during complex cognitive tasks where multiple operations may occur simultaneously. It is often used to identify temporally coherent networks (Calhoun et al., 2008a) as we discuss later.

Second, fMRI reveals that tasks other than WM can produce abnormal BOLD signal in DLPFC in schizophrenia (eg Winterer et al., 2004; Becker et al., 2008; Delawalla et al., 2008; Woodward et al., 2009). Some of these paradigms (e.g. choice reaction time; Woodward et al., 2009), are based on tasks whose performance is heritable, associated with genetic vulnerability for schizophrenia in twin studies and state-independent in patients, suggesting they are also endophenotype candidates.

Third, regions other than DLPFC, and not necessarily strongly connected to it, also behave abnormally in schizophrenia patients and their siblings (e.g. Vink, 2006; Bonner-Jackson et al., 2007). The anterior cingulate cortex is but one example of a brain region forming part of a network that is severely disrupted in schizophrenia across many cognitive paradigms ranging from the complex (e.g. conflict monitoring/cognitive interference; Rubia et al., 2001; Heckers et al., 2004; Kerns et al., 2005) to the simple, (e.g. auditory oddball detection (AOD) (Kiehl et al., 2005; Laurens et al., 2005). Additionally other types of cognitive tasks such as sentence completion also provoke abnormal network BOLD activation in unaffected siblings of schizophrenia patients (e.g. Whalley et al., 2005).

These network-related abnormalities in general could represent an underlying, unifying issue of central importance to schizophrenia, for example an abnormality in underlying dopaminergic "tuning" or efficient signal transduction.

Finally, as would be expected of an endophenotype, a genetic context for WM fMRI studies in schizophrenia is now emerging; such studies to date have generally examined a single risk gene, (e.g. Egan et al., 2001). Callicott et al. (2003b) examined effects of COMT met/val genotype on PFC fMRI activation in several performance-matched diagnostic groups, during an N-back task. Irrespective of diagnosis (schizophrenia, unaffected sib, control), met allele load predicted more efficient physiological response (less PFC BOLD activation) in the 2-back condition. In other words, "the group with relatively more cortical dopamine available at the synapse (i.e. met homozygotes) had relatively greater behavioral "bang" for its physiological "buck". In both cohorts, siblings and schizophrenia patients showed increased DLPFC activation (inefficiency) relative to controls, despite comparable performance, suggesting heritability of inefficient PFC activation. The fact that inefficient DLPFC activation is not straightforwardly correlated

with abnormal WM performance in relatives and is associated with schizophrenia risk genes such as COMT polymorphisms, supports its utility as a presumptive endophenotype as also suggested by Goldberg et al. (2003).

There are parallels to the above, for example that allelic variation in putative schizophrenia risk gene SNPs also influence hippocampal activation during several cognitive fMRI tasks; as do a $Ser^{704}Cys$ SNP of the disrupted in schizophrenia-1 (DISC1) gene, and a common variant of the brain-derived neurotrophic factor gene, (Egan et al., 2003; Pezawas et al., 2004; Callicott et al., 2005; Di Giorgio et al., 2008).

To summarize the above, Karlsgodt et al. (2008) summarized that evidence across such studies implicates neurodevelopmental disruption of brain connectivity in schizophrenia likely involving susceptibility genes affecting development of intra- and inter-regional connectivity. Similarly Tan et al. (2007) suggests that a final common effect of dopaminergic (e.g. COMT) and glutamatergic (e.g. GRM3) risk genes on "macrocircuit stability and functional efficiency" affect cortical signaling and ultimately processing strategies, leading to the characteristic cognitive deficits in schizophrenia. Thus, patients engage larger networks of cortical regions during task performance, consistent with "reduced signal-to-noise components and the recruitment of compensatory networks".

OTHER APPROACHES

There are problems inherent in the predominant fMRI research strategy of focusing on challenge tasks based in cognitive domains where schizophrenia patients are behaviorally impaired, such as WM. As we discussed earlier, numerous illness-related factors confound abnormal task-related brain activation and poor task performance. One solution to this problem has been to use easy or minimal-effort paradigms such as oddball tasks in which patients and controls perform at comparable levels of accuracy, or even imaging during rest, when there is no task (such as resting state/default mode paradigms), requiring no cognitive effort on the part of the subject (e.g. Greicius et al., 2004; Bluhm et al., 2007; Garrity et al., 2007).

USE OF "SIMPLER" TASKS SUCH AS THE AUDITORY ODDBALL

Several groups have studied the AOD paradigm, originally developed in event-related potential studies, in detail using fMRI because it is a straightforward, relatively simple task activating multiple, diverse cortical and subcortical regions and is abnormal in schizophrenia patients and their unaffected relatives (Winterer et al., 2003a,b). Functional brain imaging studies took advantage of this existing task which could be extended informatively with the unique capabilities of functional MRI. Despite the fact that patients can perform the task almost as well (as accurately if slightly slower than) healthy controls, GLM-derived activation patterns are abnormal in most schizophrenia patients (Calhoun et al., 2004; Kiehl et al., 2005; Calhoun et al., 2006a,b,c; Garrity et al., 2007; Demirci et al., 2009; Sui et al., 2009). The electrophysiological equivalent of the auditory oddball fMRI task is the auditory oddball P300 paradigm, a recognized endophenotype candidate for schizophrenia, whose activation patterns are strongly heritable, minimally influenced by illness stage or antipsychotic medication, and often abnormal in first-degree unaffected relatives (although not necessarily diagnostically specific). Future auditory oddball studies will undoubtedly explore more endophenotypic properties of fMRI response in schizophrenia such as heritability estimates, specificity of abnormal patterns to schizophrenia, responses in unaffected first-degree relatives etc. In addition to primary task-correlated BOLD patterns generally obtained through use of GLM analytic approaches, (e.g. Kiehl et al., 2005) the AOD when analyzed using Independent Component Analysis (ICA)-based approaches (e.g. Calhoun et al., 2004, 2008b), has been used as a convenient means to derive default mode data (see below).

RESTING STATE AND DEFAULT MODE NETWORK PARADIGMS

Complex cognition is not generated by local processing within a single task-engaged brain region such as DLPFC, but from widely distributed groups of brain regions acting as neural networks or circuits (Ramnani et al., 2002; Fuster, 2006). In addition to the well-documented networks underlying WM, vision, language, sensory, motor and focused attention, researchers were surprised to discover other sets of networks (typically 10 or so) unrelated to overt cognitive tasks and even present at rest when no task was being performed (Cordes et al., 2001), (so called "resting state networks" or "default mode") in which the brain idles, but there is interconnected processing of activity among major centers in the cerebral cortex (Raichle et al., 2001) discussed below. Examination of spontaneous brain activity during "rest" potentially eliminates the type of behavioral performance difference-related confounds mentioned at the start of this section and captures differences in "baseline" cognitive activity.

Characteristics of the Default Mode are listed in **Table 2**.

A major statistical approach to identifying signal from such networks is ICA. ICA and similar techniques are methods for recovering underlying signals from linear signal mixtures using higher-order statistics to determine a set of components that are maximally independent of each other. The method is "blind," so that no task-related time course information is required in the model. ICA also has the advantage of not requiring seed voxels or the use of temporal filtering, (see McKeown and Sejnowski, 1998; Broyd et al., 2009). ICA is based on the assumption of spatially independent, temporally correlated, coherent brain networks. In addition to the strong temporal correlations *within* each component/network, ICA approaches can also be used to identify also weak temporal correlations *among* these different networks. The latter relationships, as we review later, are used to assess functional network connectivity. ICA has been used to identify several temporally coherent networks present in healthy subjects either during rest or during performance of various tasks.

Table 2 | Characterization of default mode.

- Specific, anatomically defined brain network
- Most active when subject not focused on external environment or cognitive task
- One of a family of circuits active during rest
- Contains sub-networks
- Constituent regions communicate via low-frequency oscillations
- Activity diminishes when brain engages with external environment eg relative to task difficulty

This type of functional connectivity is often measured as inter-regional correlations among spontaneous fluctuations of hemodynamic activity during a "resting state" while participants lie passively in the MRI machine, but no active cognitive or behavioral demands are imposed. Initial identification of significant temporal inter-correlation among the precuneus/posterior cingulate, ventral anterior cingulate, and ventromedial prefrontal cortex (i.e., regions now defined as comprising the classic "default mode" of brain activity) (Greicius et al., 2003; Buckner et al., 2008; Broyd et al., 2009) led to interest in locating additional functionally-integrated neural networks during resting state and soon led to related fMRI research in schizophrenia. These recent reviews speculate that several mesial temporal regions may also contribute a sub-network within the default mode, but it remains unclear whether this contribution is primarily from memory-related functional studies. Investigations applying ICA or similar methods to resting state fMRI data have identified additional discrete neural circuits comprised of brain regions often engaged by higher-order cognitive tasks, including fronto-cerebellar, parietal-cerebellar, fronto-parietal, and cingulo-opercular networks (Beckmann, et al., 2005; Fransson, 2006; Dosenbach, et al., 2007; Seeley, et al., 2007). In sum, fMRI resting state research has found reproducible evidence for a "family" of 10 or more distinct networks engaged during rest (Beckmann et al., 2005; De Luca et al., 2005; Damoiseaux et al., 2006; Calhoun et al., 2008a). Resting state networks are also present during and modulated by cognitive task performance (where they are usually referred to as "default mode networks"; DMNs). Such circuits are more generally termed "temporally coherent networks" (TCN's; Calhoun et al., 2008a) and are robust, straightforwardly identified using ICA and can be consistently identified at rest and during cognitive tasks. As well as the "classic" DMN a bilateral temporal network is prominent.

The DMN is highly metabolically active, being responsible for approximately 80% of brain energy metabolism. It participates in organized baseline brain "idling" and maybe represent self-reflection, focus on internal stimuli, stream of consciousness or other activities (Gusnard et al., 2001); certainly it diminishes during task-related behaviors (Raichle et al., 2001) in a manner proportional to task difficulty (McKiernan et al., 2003). In general, the more effortful the cognitive task, the more the classic resting state/default mode network activity diminishes during task engagement, (McKiernan et al., 2003): in addition multiple "families" of TCN's also show temporal and spatial modulation during cognitive tasks versus rest. This information was used by Garrity et al. (2007), who extracted default mode activity during performance of an auditory oddball task, and showed abnormalities in schizophrenia that correlated with both positive and negative illness symptoms. While in healthy subjects the network resonated slowly and regularly, this activity in schizophrenia was increased, more irregular and correlated with positive symptoms. DMN BOLD in schizophrenia was both over-and under-active within different regions, but the entire circuit appeared unable to stabilize itself in the default mode.

Other groups have also demonstrated significant differences between schizophrenia patients and controls using resting state or default mode data, (Liang et al., 2006; Whitfield-Gabrieli et al., 2009). Consistent with its status as a putative schizophrenia endophenotype, these data reveal abnormalities in unaffected relatives of schizophrenia subjects, (Whitfield-Gabrieli et al., 2009) and are patterns are heritable (Broyd et al., 2009; Glahn et al., under review).

Combining information from separate TCNs is also useful. In a separate experiment examining diagnostic discrimination between schizophrenia, psychotic bipolar disorder and healthy controls, an approach incorporating data from both the classic default and temporal lobe modes derived from an AOD task using a leave-one-out approach, was able to achieve an average sensitivity and specificity of 90% and 95% respectively Calhoun et al. (2008b). This showed the utility of the default mode as a diagnostic classifier even when two psychotic groups were included in the analysis.

FNC AS A MEANS OF EXTENDING RESTING STATE STUDIES

As discussed above, complex cognition arises from task-related, widely distributed groups or networks of brain regions (Fuster, 2006). Functional connectivity analyses provide an opportunity to extend our knowledge regarding neural circuits. As discussed in Calhoun et al. in press (accompanying article, this volume), the profile and strength of network-to-network influences, i.e. interactions across, rather than within networks, ("functional network connectivity"; (FNC) contains useful information. ICA of fMRI is well-suited to characterize multiple functional networks because by definition the brain regions in each component have the same profile of hemodynamic signal change. Demirci et al. (2009) and Jafri et al. (2008) recently examined functional network connectivity in controls and schizophrenia patients during resting state alone or in addition to WM and attention tasks, to examine the weaker temporal relationships (such as lags) between circuits. Such studies not only found evidence for measurable, directed influences among large-scale distributed functional networks in controls, but also found that schizophrenia was characterized by widespread disruption, greater dependency, and greater variability of network inter-relationships, possibly reflecting cortical processing deficiencies. Schizophrenia subjects showed significantly higher correlations than controls among many of the dominant resting state networks (see additional details in Calhoun et al., in press).

In sum, several different functional networks identified through ICA of BOLD activation appear to be important indicators of schizophrenia pathophysiology. As suggested by Mesulam (1998) emerging neural network research indicates that these circuits are commonly engaged across many tasks in both schizophrenia and control groups, including networks subserving complex focused attention, "brain idling", working memory/executive decision-making, set maintenance and language (1) prefrontal-parietal, (2) cingulate-opercular, (3) temporal lobe and (4) the classic "default mode" network). These circuits are focused around four major anatomic hubs already implicated in schizophrenia and suggest illness-related deficits might arise from abnormalities in the quality or strength of functional connections among major nodes. Earlier we discussed one of these networks, the prefrontal-parietal, extensively in the context of WM; thus these two apparently separate lines of research (complex "stress test" and "no task") converge as can analysis methods, (Arfakanis et al., 2000). Therefore, an overarching hypothesis is that the "disconnection syndrome" in schizophrenia represents miscommunication and/or disconnection

between these key networks, which can be best understood through analytic approaches that determine how structural or functional connectivity abnormalities underlie the well-documented cognitive deficits or symptomatic syndromes.

BOLD MEETS GENETICS: PROBLEMS WITH HIGH-DIMENSIONAL DATA SETS

Most of the presumed many schizophrenia risk genes remain unknown and may exert their effects epistatically. As functional MRI endophenotypes emerge, an obvious question is how to connect them to the complex patterns of emerging schizophrenia risk genes as the latter are identified (e.g. see Harrison and Weinberger, 2005), especially using newer approaches such as genome-wide association studies (GWAS). Analyzing such large, complex data sets involving the millions of gene variants and hundreds of thousands of voxels typically involved in a GWAS/functional imaging study, can rapidly overwhelm any relevant signal (Pearlson, 2009). This challenge has led to the development of new exploratory statistical techniques such as parallel independent component analysis (paraICA), (Liu et al., 2008) for analyzing such high-dimensional, multimodal data. A recent paper (Liu et al., 2009a,b) used this algorithm to identify simultaneously independent components of imaging and genetic modalities and the relationships between them.

Parallel ICA is a variant of ICA designed for multimodality processing. It extracts components using an entropy term based on information theory to maximize independence (Bell and Sejnowski, 1995) and enhances the interconnection by maximizing an inter-modality linkage function (Liu et al., 2009a,b), i.e. it extracts the intrinsic relationship between identified independent components from two distinct modalities based on higher-order statistics. The technique is readily used as an approach for revealing relationships between brain function and SNP groupings, i.e. to identify a combination of SNPs related to functional brain networks. This involves simultaneously solving three problems: revealing a set of specific independent brain functions, identifying independent SNP associations, and finding the correlative relationship (mutual information) between them Liu et al. (2008). The resulting components extracted from fMRI data can be interpreted as spatially distinct networks of brain regions expressing functional changes in different subjects to different degrees. For instance, the degree to which a given network is present may distinguish healthy subjects from schizophrenia patients. Similarly, components extracted from SNP data are distinct, independent, linear combinations of SNPs ("clusters" of functionally linked SNPs, likely representing SNPs with common interactions) that may affect certain genetic functionalities or phenotypes, or even clusters of physiologically interacting genes. Loading parameters (Liu et al., 2008, 2009a,b) which express the association for every component with each subject are calculated.

As proof of principle, using data derived from an fMRI auditory oddball task in only 43 healthy controls and 20 schizophrenia subjects (all Caucasian) the paraICA approach was able to identify (Liu et al., 2009a,b) a fronto-parietal fMRI component that significantly separated schizophrenia patients from healthy controls, and an associated 10-SNP component that also significantly separated groups, that contained several known putative schizophrenia risk genes, including DISC1, CHRNA7 and the alpha-2 adrenergic receptor gene. Thus ParaICA seems to be a sensitive technique for dealing with gene/functional circuit interactions in medium-sized data sets.

CONCLUSIONS

We have attempted to summarize briefly both where the field is currently with regard to endophenotype discovery and validation as well as related advances in model building, proceeding from the new genetic and neuroimaging tools available to the field. In this context, we contrast data derived from fMRI studies using two counterposed approaches; the dominant paradigm of "cognitive stress tests" based on cognitive tasks on which schizophrenia subjects are previously known perform poorly versus newer, resting state/default mode studies where cognitive effort is minimized, that represent conceptually different approaches to endophenotype discovery as summarized in **Table 3**. Because of the wealth of prior experiments in animals and humans on WM paradigms, a large body of data exists on WM including major regions involved, relevant neurotransmitters, possible cell types, and whether major genes are known to play a role in the process. In contrast, the major "purpose", if indeed there is one, for the default mode is still under active debate (for example see a detailed discussion in Buckner et al., 2008), and no related genetic underpinning has yet been revealed. However the very specificity of detail regarding WM is both a strength and weakness; WM may yet prove to be only a particularly marked example of a more generalized process that characterizes the fundamental pathophysiology of schizophrenia. Abnormalities in the default mode or in the ability to switch between the default mode and effortful cognitive tasks such as WM may be of greater relevance. In any event both of the approaches we delineate identify brain patterns that meet many criteria for endophenotypes in SZ, as summarized previously in **Table 1**. The gaps in that table show that not all endophenotypic criteria are met, because some needed data are not yet available. This presents an exciting challenge to researchers.

More generally, do functional neuroimaging studies perform better than other putative schizophrenia endophenotypes? No studies have yet sufficiently compared different endophenotypes in the same populations of patients, relatives and healthy controls to address this question, as well as clarifying their disease specificity, e.g. compared to psychotic bipolar disorder. Ultimately, understanding the genetic architecture of imaging endophenotypes is likely to prove extremely important in better comprehending what

Table 3 | Comparison of default mode versus "dominant" working memory functional paradigms.

	DMN/resting state paradigms	Typical WM paradigm
Ease of performance for psychiatrically ill subject	High	Low
Characterization of underlying neurotransmitter genes	Unknown	Partially delineated
Time demand of task	Low	Typically high
BOLD output ambiguated by ability to perform paradigm	No	Yes

constitutes biological risk for schizophrenia. If schizophrenia proves to be a disorder of cortical connectivity and functional imaging intermediate phenotypes have a simpler genetic architecture than the full clinical disorder, uncovering gene interactions that underpin functional disconnections is a priority. In particular, finding genes influencing DMN/RS as suggested by Meyer-Lindenberg (2009) and discovering how such genes "build" functional circuits in both the normal brain as well as how these differ in risk-related variants in schizophrenia and at-risk individuals is crucial. Several recent large-scale studies of clustering patterns of multiple endophenotypes within and between categories of psychosis, such as Consortium on the Genetics of Schizophrenia (COGS; Braff et al., 2007; Calkins et al., 2007) and The Bipolar Schizophrenia Network on Intermediate Phenotypes (B-SNIP; Thaker, 2008; Pearlson, 2009) are now addressing these questions. In addition, the field needs to take better advantage of analytic tools of great power that have become available recently and that allow problems of the degree of complexity of schizophrenia pathophysiology to be analyzed adequately. These tools include approaches such as paraICA, in which multiple genes (and perhaps their epistatic interactions; Liu et al., 2009a,b) can be modeled and the gene clusters thereby identified studied subsequently with molecular pathway tools to uncover their collective interactions in cellular processes that likely underlie schizophrenia's pathophysiology.

Other novel suggestions have been to combine multiple potential functional imaging intermediate phenotypes into "extended endophenotypes" as originally suggested by Prasad and Keshavan (2008) for structural endophenotypes. One examples of this approach for the Temporal Lobe and Default Modes was discussed earlier (e.g. Calhoun et al., 2008b). Other fruitful directions for future research should include more detailed exploration of the relationship between the WM and DMN circuits in schizophrenia- for example using FNC- this would likely provide useful information. Ultimately, dysfunction in both circuits may represent different examples of deficient cortical information processing (e.g. Callicott et al., 2003b), or the two processes may prove to be unrelated and to originate in separate pathophysiological processes.

For the reasons summarized above, the next few years are likely to see a proliferation of publications on schizophrenia endophenotypes, and among these papers dealing with the genetics of functional imaging using the two major approaches we contrast will be undoubtedly strongly represented.

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Frontal white matter integrity as an endophenotype for schizophrenia: diffusion tensor imaging in monozygotic twins and patients' nonpsychotic relatives

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Diffusion tensor imaging (DTI) provides anatomical connectivity information by examining the directional organization of white matter microstructure. Anatomical connectivity and its abnormalities may be heritable traits associated with schizophrenia. To further examine this hypothesis, two studies were conducted to compare anatomical connectivity between (a) monozygotic (MZ) twin pairs and random pairings among twins and (b) first-degree relatives of schizophrenia patients and a healthy control group. Analyses focused on frontal regions of the brain following previous findings of anatomical connectivity abnormalities associated with schizophrenia. For Study 1, eighteen MZ twin pairs (11 female pairs, age: M = 25.44, SD = 5.69) were recruited. For Study 2, twenty-two first-degree relatives of schizophrenia patients (14 females, age: M = 48.50, SD = 8.22), and 30 healthy controls (12 females, age: M = 43.83, SD = 11.39) were recruited. Fractional anisotropy (FA), a white matter directional organization metric, was measured with DTI. In Study 1, FA values were more strongly correlated between MZ twin pairs than between randomly generated pairs in genu of corpus callosum, anterior cingulum and forceps minor. In Study 2, relatives of schizophrenia patients showed reduced FA values in medial frontal white matter ($p < 0.05$, corrected). The present study suggested that anatomical connectivity in medial prefrontal cortex appeared significantly heritable within MZ twin pairs, an important criterion in the development of an endophenotype. In addition, altered medial frontal white matter integrity found in non-affected relatives of schizophrenia patients seems to suggest that reduced white matter integrity in medial frontal regions of the brain might be associated with the genetic liability to schizophrenia.

Keywords: diffusion tensor imaging , fractional anisotropy, monozygotic twin pairs, schizophrenia relatives, endophenotype, white matter, medial frontal

INTRODUCTION

Quality of brain functioning is dependent upon the proper interaction of multiple brain regions and neural networks. These interactions occur on multiple spatial and temporal scales, i.e. fast and slow communication between circumscribed and distributed brain areas. Disruption of the normal interactions between brain regions may be related to cognitive deficits and clinical symptoms found in psychiatric populations (Hoptman et al., 2004; Fujiwara et al., 2007; Manoach et al., 2007; Skelly et al., 2008; Takei et al., 2008; Camchong et al., 2009; Whitfield-Gabrieli et al., 2009).

Successful communication between brain areas depends on the underlying structure of neural networks (e.g. axonal and dendritic networks connecting brain areas). Diffusion tensor imaging (DTI) is an *in vivo* approach that has been used to look at interaction of brain regions by examining the directional organization of white matter microstructure. DTI provides information about the magnitude and direction of water diffusion within white matter tissue (Basser and Pierpaoli, 1996). Water diffusion in white matter is restricted by myelin, a lipid- and protein-rich axonal covering. Intracellular water within myelinated axons diffuses in a more directional manner compared to diffusion in unmyelinated axons. The directional properties of water diffusion can be measured with fractional anisotropy (FA), a commonly derived scalar measure of DTI. High FA values correspond to preferential diffusion along one direction, indicating a high level of tissue organization (Basser and Pierpaoli, 1996).

DTI studies examining schizophrenia have found lower levels of tissue organization, manifested as lower FA values in schizophrenia patients (Kubicki et al., 2003., 2005, 2008; Sun et al., 2003; Hoptman et al., 2004; Kanaan et al., 2005; Fujiwara et al., 2007; Manoach et al., 2007; Schlosser et al., 2007; Cheung et al., 2008; Skelly et al., 2008; Takei et al., 2008; Camchong et al., 2009; Ellison-Wright and Bullmore, 2009) and in individuals at high risk for developing the disease (Hoptman et al., 2008; Munoz Maniega et al., 2008; Karlsgodt et al., 2009) when compared to controls. Reduced white matter connectivity has been found in a number of regions in schizophrenia patients including fornix, genu and splenium of corpus callosum, anterior cingulum bundle, superior occipito-frontal fasciculus, internal capsule and arcuate fasciculus (Kubicki et al., 2003, 2005, 2008; Sun et al., 2003; Fujiwara et al., 2007; Cheung et al., 2008).

Based on findings from a recent study conducted by our group (Camchong et al., 2009), this current study focused only on connectivity abnormalities in medial frontal regions of the brain (genu

of corpus callosum, anterior cingulum bundle). Medial frontal abnormalities have been consistently found in both white matter and adjacent gray matter of schizophrenia patients (Sun et al., 2003; Fujiwara et al., 2007; Kubicki et al., 2008; Kyriakopoulos et al., 2008a; Camchong et al., 2009; Fitzsimmons et al., 2009). The investigation of altered medial prefrontal cortex found in schizophrenia patients is important because previous studies have found significant associations between severity of behavioral abnormalities (such as severity of psychopathology and severity of cognitive dysfunction) and altered medial prefrontal cortex connectivity (Hoptman et al., 2004; Manoach et al., 2007; Skelly et al., 2008; Takei et al., 2008; Camchong et al., 2009). In the current study, we were particularly interested in examining the possibility of considering altered anatomical connectivity in medial prefrontal cortex a heritable biological marker, or endophenotype, for schizophrenia.

An endophenotype is a measurable trait intermediate between the clinical manifestation of the disorder and its underlying genes (Gottesman and Gould, 2003). The endophenotype, then, is putatively a less complex correlate of the disorder than are clinical symptoms, is closer to gene action, and can aid in discovering the disorder's genetic etiology. White matter connectivity abnormalities in schizophrenia patients, indeed, meet the first criterion (Gottesman and Gould, 2003) proposed to be necessary for status as an endophenotype: that the trait is associated with the illness in the population (Sun et al., 2003; Fujiwara et al., 2007; Kubicki et al., 2008; Camchong et al., 2009). In the current study we will focus on two additional criteria necessary for endophenotype status (Gottesman and Gould, 2003): that the trait is heritable and that the endophenotype is found in non-affected family members at a higher rate than in the general population.

In order to investigate whether medial frontal white matter abnormalities are heritable, the correlation between healthy family members may be examined. Family members that share the highest degree of genetic makeup are monozygotic (MZ) twins. By examining the degree of similarities or correlation of white matter integrity between MZ twins we can explore the degree of heritability of this trait. To our knowledge, there are no studies that have examined heritability of white matter integrity in twin pairs.

Endophenotype status also requires that non-affected family members of schizophrenia patients show medial frontal white matter abnormalities. Findings of connectivity abnormalities in patients' relatives, however, are not very consistent; although frontal regions are usually implicated (Hoptman et al., 2008). A study by Hoptman et al. (2008) found that relatives of schizophrenia patients had reduced FA in white matter adjacent to inferior frontal gyrus, posterior cingulate and angular gyri. Munoz Maniega et al. (2008), focusing on four discrete regions of interest, found reduced FA in anterior limb of the internal capsule in relatives of schizophrenia patients, a white matter tract that has connections between the thalamus and frontal lobe. Karlsgodt et al. (2009), who also focused on specific regions of interest, found reduced FA in superior longitudinal fasciculus, a fronto-parietal connection, of relatives of schizophrenia patients. Taken together, these findings suggest that altered frontal white matter connectivity indeed shows promise as an endophenotype for schizophrenia. Medial frontal regions, in particular, may be an important area on which to focus, as connectivity deficits have been consistently found here (Sun et al., 2003; Fujiwara et al., 2007; Kubicki et al., 2008; Kyriakopoulos et al., 2008b; Camchong et al., 2009), and this region has been shown to be involved in certain clinical and cognitive deficiencies present in schizophrenia patients (Manoach et al., 2007; Camchong et al., 2009; Whitfield-Gabrieli et al., 2009). Based on this literature, the present study focused the examination of white matter integrity on this region as a confirmatory analysis. An exploratory analysis was also conducted looking for group differences in the whole brain.

In order to further explore the hypothesis that white matter disorganization in medial frontal regions is a schizophrenia-related endophenotype, we conducted two studies. Study 1 examined the degree of correlation (i.e. heritability) of white matter connectivity, as indexed by DTI-derived FA values, in medial frontal regions of healthy MZ twins. Heritability is arguably one of the most important criteria to be met by a potential endophenotype (Gottesman and Gould, 2003). Given that MZ twins share nearly identical genetic loadings for the presence of any particular physical trait, the degree of similarity between members of a twin pair reveals the importance of genes for that trait, assuming no assertive mating among the twins' parents for traits associated with FA values, and a minimal contribution of shared environmental factors. With regard to white matter organization, therefore, we hypothesized that MZ twins would have a stronger degree of correlation than in pairs of non-related individuals (i.e. white matter connectivity would be heritable). Study 2 compared white matter connectivity deficits between first-degree biological relatives of schizophrenia patients and a control group. We hypothesized that the relatives would show similar anatomical connectivity abnormalities as the patients when compared to the control group; these abnormalities, however, would be found to a lesser degree in relatives than what has been previously found in schizophrenia patients.

MATERIALS AND METHODS

STUDY 1

Participants

Eighteen MZ twin pairs (11 female pairs, age: $M = 25.44$, SD = 5.69) were recruited from a twin registry from the University of Minnesota. All participants were free of neurological problems. Exclusion factors were DSM-IV criteria for Alcohol or Substance Abuse or Dependence within 3 months prior to scanning; significant medical illness; or head injury resulting in loss of consciousness exceeding 30 min.

DTI data acquisition and analysis

All subjects were scanned using a research-dedicated Siemens Trio 3 Tesla scanner (Erlangen, Germany) located at the Center for Magnetic Resonance Research at the University of Minnesota. A high-resolution T1-weighted anatomical image was acquired using a magnetization prepared rapid gradient echo sequence. DTI data were acquired axially using a dual spin echo, single shot, pulsed gradient, echo planar imagine (EPI) sequence (TR = 6.2 s, TE = 85 ms, 55 slices, voxel size = 2.5 mm × 2.5 mm × 2.5 mm, 0 mm skip, FOV = 240 mm, *b* value = 1000 s/mm2). Diffusion was measured along 30 directions.

Data were preprocessed with FDT (FMRIB's Diffusion Toolbox) (Behrens et al., 2003). Data was corrected for effects of head movement and eddy currents by using affine registration to a reference

volume (Reese et al., 2003). Voxel-wise statistical analysis of the FA data was carried out using TBSS (Tract-Based Spatial Statistics) (Smith et al., 2006), part of FSL (Smith et al., 2004). First, raw DTI data was brain-extracted using BET, and then FA images were created by fitting a tensor model to the raw diffusion data using FDT. All subjects' FA data were then aligned into a common space (Montreal Neurological Institute-152 brain) (Mazziotta et al., 1995) using the nonlinear registration IRTK (Rueckert et al., 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centers of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxel-wise cross-subject statistics.

In order to examine medial frontal similarities between MZ twins, a region of interest (ROI) was defined that included cingulum bundle and genu of corpus callosum. The ROI was created by overlaying the TBSS-generated skeleton with the John Hopkins University (JHU) DTI-based probabilistic atlas. To correct for multiple comparisons, a randomization test on correlation coefficients was used[1] (Howell, 2001, 2007) to generate a sampling distribution to test the significance of 15 voxels that showed the highest cross-twin correlations within the mask. In this analysis, twin 1 FA values were held constant, while twin 2 FA values were permuted 100,000 times in order to build a sampling distribution of r. The randomization program by Howell (Howell, 2001) provided a sample distribution of r with 100,000 cases for each voxel, thereby providing a probability that the obtained r for the original comparison is due by chance (uncorrected p-values).

STUDY 2

Participants

Twenty-two first-degree relatives of schizophrenia patients (14 females, age: $M = 48.50$, SD = 8.22), and 30 healthy controls (12 females, age: $M = 43.83$, SD = 11.39) were recruited. Three of the first-degree relatives of schizophrenia patients were parents, the remaining nineteen relatives were siblings. These participants were recruited from a larger, broader family study conducted through the Minneapolis VA Medical Center if they fulfilled the criteria outlined below. Participants were excluded if English was a second language, had an IQ less than 70 or a diagnosis of mental retardation, current alcohol or drug abuse, current drug dependence, a current or past central nervous system disease or condition, a medical condition or disease with likely significant central nervous system effects, history of head injury with skull fracture or loss of consciousness of greater than 30 min, a physical problem that would render study measures difficult or impossible, a history of electroconvulsive therapy, and an age less than 18 or greater than 60. Participants were additionally excluded for a current major depressive episode, current or previous use of anti-psychotic medications, a personal history of psychosis or bipolar affective disorder, or an Axis II Cluster A personality disorder. Lastly, controls were further excluded for a family history of psychosis or bipolar affective disorder. The Veteran's Affairs Medical Center and University of Minnesota Institution Review Boards approved the protocol.

DTI acquisition and analysis

Data acquisition parameters were the same as in Study 1 for the first 12 relatives of schizophrenia patients and the first 16 healthy controls. For the remaining 10 relatives and 14 healthy controls DTI data were acquired axially using a dual spin echo, single shot, pulsed gradient, EPI sequence (TR = 7.0 s, TE = 87 ms, 55 slices, voxel size = 2.5 mm × 2.5 mm × 2.5 mm, 0 mm skip, FOV = 325 mm, b value = 1000 s/mm2). Diffusion was measured along 30 directions. Data preprocessing was the same as in Study 1.

Voxel-wise t-test within the ROI (same as in Study 1) was conducted to examine regional group differences with Randomise from FSL51. Randomise[2] is a permutation program that corrects for multiple comparisons by using the null distribution of the max (across the image) cluster size (Nichols and Holmes, 2002). Randomise enables modeling and inference using a cluster-based thresholding (critical t-value of 1.697). Effects of scanner and effects of age were added to the model as nuisance variables. Whole brain voxel-wise t-test was conducted as an exploratory analysis to look for group differences with Randomise.

The program tbss_fill[3] from FSL was used for illustration purposes of final results for both studies. Tbss_fill thickens the thresholded stats image, filling it out into the local "tracts" seen in mean_FA (See **Figure 1**).

RESULTS

STUDY 1

Voxels found to be correlated between MZ twin pairs included genu of corpus callosum, anterior cingulum and white matter adjacent to medial frontal cortex (see **Figure 1** and **Table 1**). FA values were more strongly correlated between MZ twin pairs than between randomly generated pairs in these regions (mean of obtained $r = 0.58$; mean of p value = 0.02).

STUDY 2

Mean ages in relatives ($M = 48.50$, SD = 8.22) were not significantly different from controls ($M = 43.83$, SD = 11.39) [$t(2, 50) = 1.633$, $p = 0.11$]. Between-groups t-test revealed significant differences in two discrete clusters in right genu of corpus callosum (See **Figure 1** and **Table 2**). Relatives of schizophrenia patients had significantly lower FA values than controls in this region ($p < 0.05$, corrected, t-values were greater or equal to 1.697). There were no significant effects of scanner covariate or age covariate and white matter FA. There were no group differences as a result of whole brain voxel-wise t-test analysis.

DISCUSSION

The present study investigated the degree to which white matter disorganization in medial frontal regions is a biological marker or endophenotype associated with schizophrenia. White matter connectivity in medial frontal regions was examined (1) in healthy MZ twins in order to address heritability of white matter connectivity in this region and (2) in first-degree biological relatives of schizophrenia patients to investigate whether individuals at risk for developing the disease have similar alterations in frontal white matter

[1] http://www.uvm.edu/~dhowell/StatPages/Resampling/RandomCorr/randomization_Correlation.html

[2] http://www.fmrib.ox.ac.uk/fsl/randomise/index.html

[3] http://www.fmrib.ox.ac.uk/fsl/tbss/index.html#display

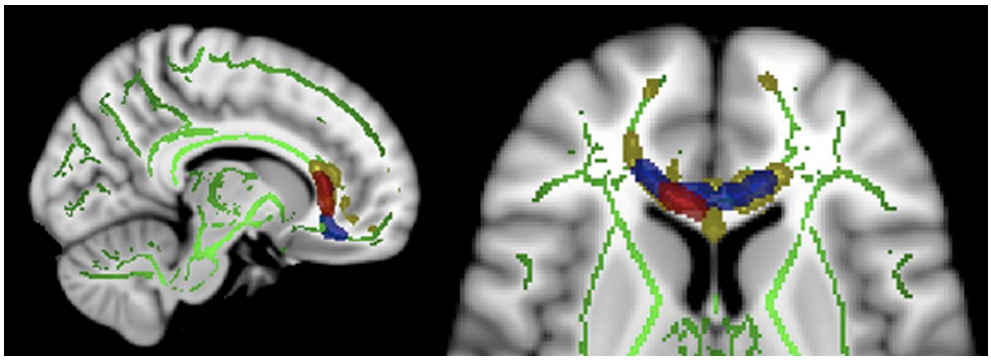

FIGURE 1 | Sagittal and axial views of Tract-Based Spatial Statistics results (MNI coordinates mm: *x* = 11 and *z* = 7 respectively). Green: mean FA (fractional anisotropy) skeleton. **Yellow**: higher correlation of FA values between monozygotic twin pairs compared to randomly generated pairs. **Blue**: reduced FA values found in schizophrenia patients compared to controls reported in a previous study (Camchong et al., 2009). **Red**: reduced FA values found in relatives of SZ patients compared to controls in the current study. Images are radiologically oriented (left is right).

Table 1 | MNI (Montreal Neurological Institute) (Mazziotta et al., 1995) coordinates for regions showing high correlations between monozygotic twin pairs.

John Hopkins University white matter atlas		MNI coordinates *x, y, z*	Volume – microliters (mm^3)
Genu of corpus callosum	Left	–12, 33, 5	337
		–1, 25, 5	37
	Right	13, 30, 11	324
Anterior cingulum	Left	–7, 32, 12	120
	Right	14, 45, 6	61
Forceps minor	Left	–15, 54, –5	55
		–17, 39, 16	54
	Right	13, 34, 17	52
		17, 50, 18	52

Table 2 | MNI (Montreal Neurological Institute) (Mazziotta et al., 1995) coordinates for regions showing reduced FA values in relatives of schizophrenia patients when compared to controls.

John Hopkins University atlas		MNI coordinates *x, y, z*	Volume – microliters (mm^3)
Genu of corpus callosum	Right	8, 28, 7	137
		15, 36, 0	34

connectivity previously found in schizophrenia patients (Sun et al., 2003; Fujiwara et al., 2007; Kubicki et al., 2008; Kyriakopoulos et al., 2008b; Camchong et al., 2009; Fitzsimmons et al., 2009).

To our knowledge, this is the first study that examined heritability of white matter integrity in MZ twin pairs. Our hypothesis proposing that MZ twins would have a stronger degree of correlation than in pairs of non-related individuals was supported, suggesting that white matter connectivity in frontal regions is moderately heritable, an important criterion in the development of an endophenotype. As shown in **Figure 1**, regions that have previously shown to have reduced white matter integrity in individuals with schizophrenia (Camchong et al., 2009) overlapped regions that were found to be highly correlated between MZ twin pairs, suggesting that schizophrenia-associated reduced white matter integrity in this region may be a heritable trait.

To further investigate the possibility that white matter disorganization in medial frontal regions is a schizophrenia-related endophenotype, white matter connectivity was examined in first-degree biological relatives of schizophrenia patients. Biological relatives of schizophrenia patients represent a sample of individuals at risk for developing the disease, without the confounding effects of the manifestation of the disease itself. Since present results showed that relatives of schizophrenia patients had frontal white matter connectivity abnormalities previously found in schizophrenia patients, these abnormalities might be related to the risk for developing the disease, and not to specific factors of the disease process itself such as symptom subtypes, illness duration, and/or medication effects. It should also be noted that regions previously found to have altered white matter integrity in schizophrenia patients (Camchong et al., 2009) are more widespread than in the relatives of schizophrenia patients (see **Figure 1**), suggesting that these white matter alterations are found in a lesser degree in individuals at risk for developing the disease than in patients.

Frontal white matter structures (genu of corpus callosum, anterior cingulum and forceps minor) found to have reduced FA in relatives in the present study connect lateral and medial surfaces of the frontal lobes and connect the left and right hemisphere through the corpus callosum. Evidence from studies on schizophrenia patients is consistent with altered brain connectivity in frontal regions found in the present study. In addition, previous studies have proposed a link between severity of symptomatology as well as cognition deficits and altered frontal brain connectivity (Manoach et al., 2007; Kubicki et al., 2008; Skelly et al., 2008; Takei et al., 2008; Camchong et al., 2009; Spoletini et al., 2009). Taken together, frontal regions that have shown altered white matter integrity in relatives of schizophrenia patients in the present study as well as in schizophrenia patients

in previous studies (see **Figure 1**) (Sun et al., 2003; Fujiwara et al., 2007; Kubicki et al., 2008; Kyriakopoulos et al., 2008b; Camchong et al., 2009; Fitzsimmons et al., 2009), might be effective indicators of disease risk (endophenotype), because they manifest as a function of shared genes (not disease state).

There are four improvements related to research design applicable to this study. First, heritability of frontal white matter connectivity could be better addressed by examining groups with different degrees of shared genes. Future studies including dizygotic twins and siblings would add to the present findings by investigating parametric variations of genetic overlap. Similarly, a second caveat is that our sample representing individuals with a genetic liability to schizophrenia had potentially different degrees of relationship with the schizophrenia patients (parents, offspring and siblings). As a result, there is potentially greater heterogeneity of genetic liability in the present study as well as a large distribution of age in the relative sample. Third, the analysis of schizophrenia patients would have added to the results of the current study by allowing a direct comparison to relatives. The examination of relatives of schizophrenia patients, however, has the distinct advantage of not confounding the results with effects of antipsychotic medications and/or manifestation of the disease that schizophrenia patients would add. Fourth, the present study used a cross-sectional design with the relatives of schizophrenia patients. Future studies examining changes in frontal white matter integrity across time in individuals at risk for developing schizophrenia (tracking relatives who develop or don't develop the disease later on) would add to the schizophrenia literature.

In summary, the present study reports on the degree to which white matter disorganization in medial frontal regions is a schizophrenia-related endophenotype. The present study adds to the schizophrenia literature by providing preliminary evidence proposing frontal white matter integrity as a potential biological marker for schizophrenia based on Gottesman and Gould endophenotype criteria (Gottesman and Gould, 2003). Previous studies have shown that altered frontal white matter is associated with schizophrenia (Sun et al., 2003; Fujiwara et al., 2007; Kubicki et al., 2008; Kyriakopoulos et al., 2008b; Camchong et al., 2009; Fitzsimmons et al., 2009). Second, frontal white matter integrity showed to be heritable within the MZ twin sample. Third, altered frontal white matter integrity was found in nonaffected family members at a higher rate than in the general population. It seems, therefore, that reduced white matter integrity in frontal regions of the brain is a heritable trait that appears to be associated with the genetic liability to schizophrenia.

Understanding brain abnormalities, such as frontal white matter connectivity alterations examined in the present study, aids in identifying traits that suggest genetic liability to schizophrenia because these physiological alterations are more intrinsically related to genetic alterations in schizophrenia patients than symptoms and cognition. Measures of frontal connectivity (such as fractional anisotropy measures) may be used in quantitative trait loci analyses in the search for schizophrenia genes. Future studies combining neuroimaging methods, neuropsychological assessment and molecular genetic assessment on participants with different degrees of genetic susceptibility to schizophrenia (patients, first and second degree relatives) will have a maximized power for identifying schizophrenia genes.

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Cognitive functioning in major depression – a summary

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The aim of the present paper is to summarize the research during the past decade regarding cognitive functioning in Major Depressive Disorder (MDD). Cognitive impairment in the acute phase of illness has been frequently reported. The findings are shown in different cognitive domains, such as executive functions, attention, memory and psychomotor speed. Fewer reports have investigated cognitive functioning in MDD in longitudinal studies. Some longitudinal reports show that the impairment observed in the acute phase of illness may be long lasting despite symptom reduction and recovery. However, findings regarding cognitive functioning in depression are divergent. Factors that might contribute to the divergent findings, such as depression subtype, severity and comorbidity are discussed. Clinical implications and focus of future research directions is highlighted.In conclusion, depression is associated with cognitive impairment in the acute phase of illness, and some reports indicate that this impairment might be long lasting despite symptom reduction and recovery.

Keywords: major depression, cognitive functioning, impairment, acute phase, long-lasting

INTRODUCTION

MDD is the most prevalent of all mental disorders with an estimated life prevalence as high as 13.5–21.2% (Kessler and Walters, 1998; Turner and Gil, 2002; Kessler et al., 2005). Moreover, at any time as many as 5% of the population suffers from depression (Murphy et al., 2000). Together with schizophrenia, depression is responsible for 60% of all suicides worldwide and is predicted to be the second largest cause of disability in year 2020, for all ages and both genders (World Health Organization, [WHO], 2009). Regarding course of recovery it has been reported that only 20% of MDD patients recover and remain continuously well, while as many as 20% estimates to either commit suicide or always be incapacitated. The remaining 60% will recover but have further episodes (Hollon and Shelton, 2001).

Historically, MDD was seen as an episodic disorder but recent findings have indicated that developing a chronic course of the disease has been underestimated (Rush, 2001). MDD is associated with a high relapse risk, found to be highest during the first year after a depressive episode (Mueller et al., 1999). Moreover, 50% of depressed patients experience a relapse within 2 years after their first episode, and 80% will experience more than one depressive episode during their life course (Mueller et al., 1999).

Due to the presented magnitude of this disorder, consequences are significant both at an individual level and for society. Disability in life functioning is a serious feature concerning Major Depressive Disorder (MDD) and a number of studies suggests that MDD is associated with significant disability and poorer quality of life (see review Papakostas et al., 2004). Numerous MDD patients experience that maintaining job performance at an acceptable level is difficult or impossible. Many have problems in fully participating in social and/or family life, and further they have problems in meeting other expectations from the society.

Although depression traditionally is seen as affective in nature, the last decades research have shown that depression is associated with a considerably and important disturbance in cognitive functioning.

MATERIALS AND METHODS

This summary is based on computerized searches of Medline, PsychINFO and PsychArticles, exclusively articles published since 2000, using the terms DEPRESSION/MAJOR DEPRESSION, COGNITIVE FUNCTION, ACUTE PHASE, LONGITUDINAL in combination. In addition reference lists were also examined for further relevant studies. This summary is not all-inclusive, the selection of articles reflects the authors evaluation of important themes in this area of research.

COGNITIVE IMPAIRMENT IN DEPRESSIVE DISORDERS – EVIDENCE OVER THE PAST DECADE

Research during the past decade has mainly focused on cognitive functioning in the severe phase of depression, and today it is widely accepted that the disease is characterized by cognitive impairment in the acute state (see review Austin et al., 2001; Taylor Tavares et al., 2003; see review Castaneda et al., 2008). There are reports of findings in different cognitive domains, such as executive functions (EF), attention, memory and psychomotor speed (Austin et al., 2001; Castaneda et al., 2008).

EXECUTIVE FUNCTIONING IN THE ACUTE PHASE OF ILLNESS

There is no clear consensus regarding the definition of EF however, most studies have included components such as set-shifting, inhibition, working memory, fluency (Pennington and Ozonoff, 1996), planning and problem solving (Fossati et al., 2001) when measuring EF. Elliott (2003) defines EF as "complex cognitive processing requiring the co-ordination of several sub processes to achieve a particular goal". According to this view, EF are those involved in problem solving, modifying behavior in the light of new information, generating strategies or sequencing complex actions. Impairment in EF has been frequently reported in acute phase of MDD (see review Harvey et al., 2004; Rogers et al., 2004; Stordal et al., 2004) and deficits have been shown on tests measuring inhibition

(Den Hartog et al., 2003; Markela-Lerenc et al., 2006; Gohier et al., 2009), problem solving and planning (Naismith et al., 2003), mental flexibility (Naismith et al., 2003; Airaksinen et al., 2004), verbal fluency (Reiches and Neu, 2000; Ravnkilde et al., 2002) decision making (Chamberlain and Sahakian, 2006) and working memory (Egeland et al., 2003b; Naismith et al., 2003; Rose and Ebmeier, 2006; Taylor Tavares et al., 2007), or the ability to inhibit one source of information and at the same time facilitate processing of another source of information (Hugdahl et al., 2009) (**Table 1**). More specifically it has been suggested that the inability to shift mental set is the most prominent EF impairment in MDD patients (Austin et al., 2001). Opposed to these findings, others have reported MDD patients to show normal performances in multiple aspects of EF (Grant et al., 2001; Landrø et al., 2001; Vythilingam et al., 2004; Stordal et al., 2005).

In sum, several studies have during the last decade presented firm evidence of EF impairment in the acute phase of depression, however factors contributing to the various impairment described in the literature must be indentified in a larger degree.

ATTENTION DEFICITS IN THE ACUTE PHASE OF ILLNESS

Several recent studies have reported MDD patients to show deficits on a variety of attention related tasks (Cohen et al., 2001; Landrø et al., 2001; Koetsier et al., 2002; Liu, et al., 2002; Ravnkilde et al., 2002; Hammar et al., 2003a; Porter et al., 2003; Lampe et al., 2004; Keilp et al., 2008; Simons et al., 2009) though the nature of the impairment is difficult to define as various studies investigate different aspects of this concept. Moreover, attention is closely related to other cognitive domains, especially psychomotor speed and EF. It has been suggested that attention can be divided into processing speed, selective attention and automatic processing; selective attention being a part of EF (Brebion et al., 2000; Egeland et al., 2003a), thus a frontal lobe function (Landrø et al., 2001). It has been shown that MDD patients are impaired on effortful attention related tasks, whereas normal performance is shown on automatic processing (Hammar, 2003; Hammar et al., 2003a).

It has been found that MDD patients show impairment on speeded measures however; remain unimpaired on selective attention (Pardo et al., 2006). Further, there have been studies reporting no impairment in attention in mild to moderate MDD patients (Grant et al., 2001) or MDD patients (Harvey et al., 2004; Lampe et al., 2004). The divergent results reported in the domain of attention have been suggested to be caused by a too simple attention model that does not differentiate between processing speed on the one hand, and the ability to select relevant stimuli and resist distraction on the other (Egeland et al., 2003a).

In sum, impairment in attention related tasks is frequently reported in the acute phase of MDD. An important discussion is whether specific aspects of attention are more vulnerable, and what impact these attention deficits have for daily life functioning, treatment and recovery in this patient group.

Table 1 | Findings of impairment within the cognitive domain of EF in the acute phase of depression.

Aspect of impairment in the acute phase	References
Inhibition	Den Hartog et al. (2003); Markela-Lerenc et al. (2006); Gohier et al. (2009); Hugdahl et al. (2009)
Problem solving and planning	Naismith et al. (2003)
Mental flexibility	Naismith et al. (2003); Airaksinen et al. (2004)
Verbal fluency	Reischies and Neu (2000); Ravnkilde et al. (2002)
Decision making	Chamberlain and Sahakian (2006)
Working memory	Egeland et al. (2003b); Naismith et al. (2003); Rose and Ebmeier (2006); Taylor Tavares et al. (2007)

MEMORY DEFICITS IN THE ACUTE PHASE OF ILLNESS

The cognitive domain of memory has been closely related to MDD. Memory is a complex concept involving several different processes. Consequently, various neuropsychological methods are used when different memory processes are investigated. Studies investigating memory have for instance distinguished between episodic and semantic memory, implicit and explicit memory and immediate and delayed memory, the latter being further divided into free and cued recall. Moreover, visual memory has usually been separated from verbal memory (Moscovitch, 1992).

Numerous studies have reported an association between MDD and memory impairments (Landrø et al., 2001; Fossati et al., 2002; Ravnkilde et al., 2002; Egeland et al., 2003b; Porter et al., 2003; Airaksinen et al., 2004; Campbell and MacQueen, 2004; Vythilingam et al., 2004; Matthews et al., 2008) (**Table 2**) however, the relationship is not clear. Studies have found MDD patients to be impaired in both verbal and visual memory (Reischies and Neu, 2000; Naismith et al., 2003), verbal delayed memory and verbal percent retention, however not in immediate verbal memory or visual memory (Vythilingam et al., 2004). Somewhat opposed to this, some have found immediate and delayed visuo-spatial memory to be impaired whilst immediate and long-term verbal declarative memory was preserved (Porter et al., 2003). Wang et al. (2006) found no impairment in first ever or recurrent depressed young adults compared to controls in verbal memory. Findings have also shown normal performance on tasks assessing verbal short-term memory and nonverbal long-term memory, whilst verbal working and long-term memory are impaired (Landrø et al., 2001). In contrast there are studies reporting primarily no impairment in MDD patients on tasks assessing memory (Grant et al., 2001; Barch et al., 2003; Den Hartog et al., 2003; Harvey et al., 2004).

In conclusion, memory impairment is frequently reported in the acute phase of MDD, however the nature and the mechanisms behind this impairment is somewhat unclear.

NEUROPSYCHOLOGICAL PROFILE IN THE ACUTE PHASE

Despite numerous of studies investigating cognitive functioning in MDD there is no agreement upon a conclusive neuropsychological profile characterizing depression. However, three hypotheses have been postulated in order to explain the cognitive impairment in this disorder. First, a global-diffuse hypothesis, which states that MDD patients show a generally lowered cognitive profile, suggesting a global-diffuse impairment on a range of cognitive domains (Veiel,

Table 2 | Findings of impairment within the cognitive domain of memory in the acute phase of depression.

Aspect of impairment in the acute phase	References
Verbal memory	Naismith et al. (2003); Reischies and Neu (2000)
Visual memory	Naismith et al. (2003); Reischies and Neu (2000)
Verbal delayed memory	Vythilingam et al. (2004)
Visuo-spatial memory	Porter et al. (2003)
Verbal working memory	Landrø et al. (2001)
Verbal long term memory	Landrø et al. (2001)

1997; Landrø et al., 2001). Secondly, a hypothesis of specific cognitive impairment, suggesting that MDD is associated with pronounced impairment within specific cognitive domains, foremost in EF and memory (Austin et al., 2001; Elliott, 2002). Thirdly, regardless of domain the cognitive effort hypothesis claims that MDD patients show impairment on effortful tasks whereas they show normal functioning on automatic tasks. Automatic processing is considered to be stimulus-driven, whilst effortful processing requires attention and cognitive capacity, and is also defined as an instruction-driven process (Hasher and Zacks, 1979; Hammar et al., 2003a).

The research over the past decade show diversity in findings; no single cognitive function has been found that characterizes all depressed patients, and not all patients are impaired in the same degree. However, there is firm evidence that depressed patients as a group are characterized by cognitive impairment in the acute phase. Diversity among findings might be explained by different methodological issues, such as inclusion of patients with different severity or subtypes of depression: in example bipolar disorder, first episode of major depression, recurrent episodes, depression with psychotic features, dysthymia, in patients versus out patients etc. In addition studies investigate different age groups, apply a variety of neuropsychological tests, and have different inclusion and exclusion criterion in example regarding medications and substance abuse. Co morbid disorders may play an important role in explaining diversity in findings across studies (Baune et al., 2009) in particular co morbid anxiety (see review Levin et al., 2007). When these factors are mixed within studies, it is difficult to subtract the core of the neuropsychological impairment in depression. In example, there is strong reason to believe that first ever depressed patients might show a different cognitive profile than recurrent depressed patients. It can be difficult to determine whether a person is experiencing a first ever depressive episode, thus a throughout diagnostic screening should be a part of inclusion. All these factors might influence results and cause difficulties in agreement upon a neuropsychological profile that characterize depression in the acute phase of illness. It is highly likely that different subgroups of depressed samples show different patterns of impairment. In addition, Scheurich et al. (2008) have suggested that the cognitive impairment associated with depression can be influenced by motivational aspects. Such knowledge would further be of importance for the treatment course of depression.

Although cognitive impairment in the acute phase of MDD is well documented, the knowledge of how the impairments develop in a long-term perspective is scant. A major question, with implications for our understanding of MDD, is whether cognitive impairment manifested during periods of depression is long lasting or improves during remission and recovery.

DEPRESSION AND LONG-LASTING COGNITIVE IMPAIRMENT – A NEW FIELD OF INTEREST

A common understanding early in the literature and in clinical practice has been that cognitive impairment restores as depression heals. This assumption has been questioned the last decade. The association between cognitive function and MDD in a long-term perspective has seldom been investigated, thus longitudinal studies on this topic are few and results are divergent. Knowledge in this area is therefore limited, and there are still numerous questions regarding how cognitive functioning evolves in relation to symptom reduction and remission (**Figure 1**).

Of the longitudinal studies existing on this field several indicates that cognitive impairment seen during episodes of illness, also persists during episodes of symptom reduction (Hammar et al., 2003b; Airakinsen et al., 2006) and even in remission (Reischies and Neu, 2000; Majer et al., 2004; Weiland-Fiedler et al., 2004; Neu et al., 2005; Paelecke-Habermann et al., 2005; Smith et al., 2006; Gruber et al., 2007; Nakano et al., 2008), although some studies report no such findings (Koetsier et al., 2002; Biringer et al., 2005; Lahr et al., 2007). Other studies suggests that cognitive impairment worsens for every episode of depression (Brown et al., 1999; Sweeney et al., 2000) and that impairment observed in a nonsymptomatic phase is related to number of previous episodes of depression (Kessing, 1998). It is possible that prolonged cognitive impairment holds true for sub groups of depressed samples, thus not all patients are characterized by long-lasting impairment.

Hammar et al. (2003b) found that depressed patients showed impaired cognitive performance on cognitive demanding tasks (effortful processing) when symptomatic and that the impairment prevails after 6 months, despite significant improvement in the depression symptoms.

Studies investigating patients in remission has shown long-lasting impairment in various of cognitive functions, such as sustained attention (Majer et al., 2004; Weiland-Fiedler et al., 2004), attention and Executive Functioning (Paelecke-Habermann et al., 2005), Verbal memory and verbal fluency (Reischies and Neu, 2000; Neu et al., 2005), Executive Functioning (Smith et al., 2006; Gruber et al., 2007; Reppermund et al., 2009).

In contrast a 2-year follow-up study reported a correlation between improvement in depressive symptoms and improvement in EF, suggesting that depression related changes in EF are reversible upon remission (Biringer et al., 2005). However, MDD patients failed to improve to the level of controls at follow-up on some EF measures, and the observed improvement in the depressed patient group could be due to a general training effect which was not controlled for because of missing control group at follow up.

Gualtieri et al. (2006) found that MDD patients who are successfully treated with newer antidepressants are better cognitively than untreated patients. However, the performance was still worse than healthy controls.

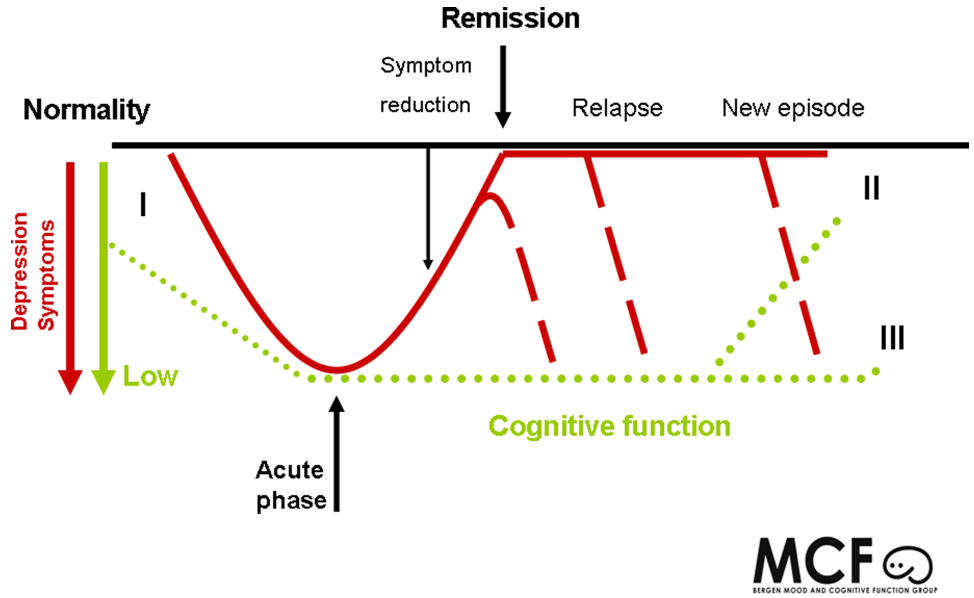

FIGURE 1 | Illustrates how the profile of cognitive impairment, the risk of relapses and symptom improvement might relate. Several aspects of the course of cognitive impairment remain to be clarified. First, does the cognitive impairment occur before the mood symptoms? See "I" in **Figure 1**. Secondly, is the time course of cognitive normalization delayed in relation to remission? See "II" in **Figure 1**. Thirdly, is long lasting cognitive impairment a predictor for enhanced relapse risk or for new episodes? See "III" in **Figure 1**. Another aspect is to clarify if various cognitive profiles are related to various subgroups of patients. Although several questions remain to be answered, the literature clearly indicates that depressed patients as a group is subject to neuropsychological impairment that may persist despite symptom reduction and remission, see "II" in **Figure 1**. Following this, another important question rises: How does long-lasting impairment in cognitive functioning affect daily life functioning in depressed individuals?

Regarding the relation between MDD and long-term cognitive functioning two different hypotheses have been proposed. Based on earlier findings the first hypothesis suggests that cognitive impairment sustains despite symptom reduction (Martinez-Aran et al., 2000; Reischies and Neu, 2000; Austin et al., 2001; Hammar et al., 2003b). The second hypothesis states that multiple depressive episodes further deteriorate cognitive impairment (Sweeney et al., 2000). There is, however, increasing indications in the recent literature that symptom reduction in depressions is not followed by cognitive improvement to a similar degree.

IMPAIRMENT IN DAILY LIFE FUNCTIONING

Depression is associated with impairment in daily life functioning (see review Papakostas et al., 2004). Several studies have investigated how depression affects daily life functioning in the acute phase of illness, thus the knowledge on this field is rather conclusive. Studies have shown that MDD affects several aspects of work performance, including productivity, task focus and days absent caused by sickness (Wang et al., 2004; Adler et al., 2006). A central aspect of life functioning is family and social relations, again shown to be impaired in depressive patients, including household strain, social irritability, financial strain, limitations in occupational functioning and poor health status (see review Papakostas et al., 2004).

Traditionally, mood symptoms have been used to explain this disability in life functioning in mood disorders. However findings indicate that improvement in daily life functioning does not follow improvement in depression symptoms to a similar degree (Adler et al., 2006; Kennedy et al., 2007). Daily life functioning has been found to be impaired even in phases of remission of depression (Angermeyer et al., 2002; Jaeger et al., 2006). Different factors could explain why improvement in depressive symptoms is not followed by improvement in daily life functioning to a similar extent. Residual symptoms, comorbidity, misdiagnosis and long-lasting cognitive impairment could be important factors associated with long-lasting impairment in daily life functioning (Kennedy et al., 2007).

Studies have found that cognitive impairment play an important role in functional recovery from depression (Jaeger et al., 2006). This has also been reported regarding bipolar disorder (Martinez-Aran et al., 2007).

The lack of knowledge on this field regarding the possible impact long-lasting cognitive impairment represents for daily life functioning in this patient group is strikingly. And there is only few studies investigating this question. This possible relationship has enormous clinical implications.

CLINICAL IMPLICATIONS

Remitted MDD patients are often expected to function at a premorbid level. However, this might not be a rightful expectation if cognitive functioning and daily life functioning is impaired in a long time course after depression. The results of this expectation may lead to frustration, low self esteem, low coping, and feelings of worthlessness for the individual involved, and in a worst case enhance the risk of relapse. Patients cognitive functioning and the impact this has on daily life functioning should be a focus in ongoing treatment. Impaired cognitive functioning affects family life, school performance, work performance and social

life. Cognitive training and rehabilitation could prove important in treating depression in the long-term course, and help prevent relapse. And important challenge is to unite research and practice, and it is of great importance that the possible long-lasting cognitive impairment associated with depression is debated in clinical settings.

FUTURE STUDIES

Cognitive impairment may be an enduring component of a chronic depression (Kennedy et al., 2007). It is evident that increased focus on longitudinal studies is necessary if the relation between MDD and cognitive function shall be further explored and understood, this mainly to improve rehabilitation conditions and prevent relapses. One of the main questions that must be further investigated is if long-lasting cognitive impairment is a risk factor for relapse episodes. If so, will cognitive training and rehabilitation be possible treatments in order to prevent new episodes. These types of questions are in today's literature still unsolved.

Moreover, MDD patients in general are a heterogeneous group and there is reason to believe that the degree of cognitive impairment is related to clinical factors such as numbers of previous episodes, duration, onset as well as treatment factors like effects of medications and hospitalization. There are many distinct combinations of symptoms that would qualify for a diagnosis. Thus, this implicates that future studies must aim to include homogenous patient groups and differ between factors such as degree of severity as well as between first episode patients, patients with recurrent episodes, bipolar diagnosis etc. Following this, an important challenge for future studies is homogenous patient groups with well described inclusion and exclusion criterion. This would make comparison across studies more precise, thus possibly answer the question of divergent findings.

Future research will have the possibility to clarify questions regarding the impact cognitive functioning in MDD patients have on life functioning in a long-term course. It is important to make clear this relationship because of the impact this might have on recovery, treatment course and outcome of the disease. Improving cognitive functioning, in example trough cognitive rehabilitation, might show crucial for work performance and occupational life in this patient group and also help patients in the therapeutic process. Identifying risk factors for relapses and new episode is of great importance in order to reduce the burden of MDD worldwide.

CONCLUDING REMARKS

During the past decade much research has focused on cognitive function in MDD, and impairment in cognitive functioning in the acute phase of illness is well documented. Less is known about the course of this impairment and several questions remain unanswered. Some studies report the impairment observed in the acute phase to be long lasting, and also persistent in phases of remission. However, there are contradictory findings on this field which might indicate that this holds true in subgroups of depressed patients, thus not describe all MDD patients. In particular there is a lack of studies investigating these questions in first ever depressed samples, and longitudinal studies following patients over several years. There is a need for studies investigating cognitive functioning in well defined homogenous patient groups longitudinally in the future.

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Brain imaging correlates of cognitive impairment in depression

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This review briefly summarises recent research on the neural basis of cognition in depression. Two broad areas are covered: emotional and non-emotional processing. We consider how research findings support models of depression based on disrupted cortico-limbic circuitry, and how modern connectivity analysis techniques can be used to test such models explicitly. Finally we discuss clinical implications of cognitive imaging in depression, and specifically the possible role for these techniques in diagnosis and treatment planning.

Keywords: depression, cognition, emotion, fMRI, antidepressants, connectivity

INTRODUCTION

Cognitive deficits, such as reduced concentration and poor memory, are hallmark features of depression listed among diagnostic symptoms (DSM-IV, American Psychiatric Association, 1994). Neuroimaging techniques provide a means to investigate neurobiological abnormalities associated with depression *in vivo*. Functional neuroimaging can identify brain areas which respond atypically to cognitive challenges, and functional magnetic resonance imaging (fMRI) is now widely used to investigate the neuronal basis of cognitive deficits in depression. Some studies have focused on cognitive challenges based on classic neuropsychological domains (e.g., executive function, memory). Others have explored cognitive mechanisms of emotional disturbance (e.g., negative bias, response to failure). Although results have not been entirely consistent, observed patterns have led to the development of neurobiological models of depression based on functionally abnormal networks. New techniques and approaches are emerging to advance our understanding of disrupted connectivity underpinning cognitive deficits in depression. Relationships between clinical features of depression and the neural basis of cognitive deficits are also being explored. Understanding these relationships has implications for diagnosis and individually tailored treatment strategies. Neuroimaging correlates of cognitive deficits may be an important biomarker for subtypes of depression that respond to different treatment approaches. In this review, we will briefly discuss recent findings with cognitive activation paradigms, before considering how newer techniques and approaches may take us forward, conceptually and clinically.

COGNITIVE ACTIVATION STUDIES IN DEPRESSION

Haldane and Frangou (2006) reviewed functional neuroimaging studies in mood disorders and concluded that most report associations between depression and increased activity in limbic regions. However, changes in cortical regions are less consistently observed and depend on the experimental paradigm used. This view is supported by another meta-analysis (Fitzgerald et al., 2006), focusing specifically on studies reporting dorsolateral prefrontal cortex (DLPFC) abnormalities. They concluded that while abnormalities were reported relatively consistently, the direction and laterality of observed changes varied depending on the challenge used. Broadly speaking, cognitive challenges used in functional neuroimaging of depression can be divided into non-emotional challenges and emotional challenges, requiring either overt or covert affective processing.

NON-EMOTIONAL COGNITIVE NEUROIMAGING IN CURRENT DEPRESSION

Executive function and working memory

Relatively few studies have examined the neural substrates of non-emotional cognitive deficits in unipolar depression. These have typically focused on executive tasks that depend on functional integrity of the prefrontal cortices. Elliott et al. (1997a) used positron emission tomography to compare neural activity in controls and depressed participants performing a complex planning task. They found that while the groups showed similar overall patterns of activity, this was globally attenuated in depressed subjects, particularly in caudate, thalamus, anterior cingulate (ACC), DLPFC and ventrolateral prefrontal cortex (VLPFC). Task performance in the depressed group was also impaired, suggesting that these attenuations may have reflected poorer performance.

By contrast, Fitzgerald et al. (2008) used a similar planning task with fMRI and reported that depressed participants showed increased activity in regions including right VLPFC, DLPFC and angular gyrus/cuneus. Unlike patients in the Elliott et al. (1997a) study, their performance accuracy was normal. This discrepancy may explain the activation differences, with Fitzgerald et al.'s

patients recruiting additional neuronal resources to achieve normal performance accuracy. Fitzgerald et al. (2008) also demonstrated increased cortical activity in a depressed group using an n-back working memory task where patients' performance was intact. Similarly, Harvey et al. (2005) found increased lateral prefrontal and ACC responses in depressed participants performing an n-back task, in the absence of any performance deficits. Wagner et al. (2006) reported enhanced cortical (VLPFC and rostral ACC) activation in depressed patients performing a Stroop cognitive control task at normal levels. Harvey et al. (2005) suggested that the increases in cortical response they observed to their n-back challenge were caused by 'cortical inefficiency'. Their participants did not show behavioural deficits, so greater cortical activity could be a neural manifestation of the greater effort required to maintain normal performance. Other studies have provided support for this theory. Langenecker et al. (2007) found that successful response inhibition in depressed subjects was associated with enhanced cortical activation. Similarly, Walter et al. (2007) assessed patients' neural response to correct trials only in a working memory task and found increased DLPFC activation. This effect was not seen when incorrect trials were included in the analysis, suggesting that matched performance is associated with increased cortical response. Several other studies have also reported prefrontal hyperactivity associated with intact performance on working memory tasks (Matsuo et al., 2007; Walsh et al., 2007).

By contrast, where patients' performance is impaired, as in the Elliott et al. (1997a) study, reduced neuronal response is typically observed in cortical regions. Okada et al. (2003) found reduced activity in left VLPFC in depressed patients during a verbal fluency task on which they also performed poorly. Hugdahl et al. (2004) found impaired performance and decreased right inferior parietal activity in depressed participants during a mental arithmetic task (although medial prefrontal function was enhanced). It therefore seems that impaired performance is associated with reduced cortical function while normal performance can only be achieved through enhanced cortical function.

However, it is not always the case that normal executive performance is associated with increased cortical activation in depression. Barch et al. (2003) reported attenuated activity in depressed participants to both word and face versions of an n-back task in bilateral thalamus, right precentral gyrus and right parietal cortex despite no behavioural deficit being observed. It should be noted that differences were not observed in the prefrontal cortex and also that performance was at, or near, ceiling. It is possible that hyperfrontality associated with intact performance is only observed for more challenging versions of tasks. These discrepancies highlight the importance of careful characterisation of the relationship between task difficulty, performance and brain response. It is also possible that differences in patient demographics, severity of illness and medication status may contribute to the observed discrepancies and these issues should be addressed systematically in future research.

Memory

Memory problems are one of the most common cognitive symptoms reported by depressed patients; however there are very few fMRI studies of non-emotional memory in depression. Bremner et al. (2004) found that conceptual memory encoding of a neutral paragraph resulted in reduced hippocampal, amygdala and ACC activation and increased right frontal gyri activation in depressed subjects. By contrast, Werner et al. (2009) reported increased parahippohampal activity at encoding and decreased activity in frontal and parietal regions during both encoding and retrieval. Performance was unimpaired. The discrepancy may reflect differences in patient characteristics, in particular their medication status (Bremner's patients were unmedicated; Werner's were mostly receiving antidepressants). Task differences are also a factor, with the studies assessing conceptual prose memory compared with associative memory for picture-word pairs. However it is also important to note that structural hippocampal pathology has been widely discussed in some depression subtypes and may represent an important confound in memory studies.

EMOTIONAL COGNITIVE NEUROIMAGING IN CURRENT DEPRESSION

Neural responses to emotional tasks in depressed patients have been more widely studied using fMRI than responses to non-emotional tasks. Studies in normal subjects have identified the amygdala as playing a key role in processing faces and facial emotions (Adolphs et al., 1994; Breiter et al., 1996; Morris et al., 1996; Haxby et al., 2000; Phan et al., 2002). Amygdala function has also been linked to enhanced memory for emotional material (Cahill et al., 1995; Canli et al., 2000) and general processing of emotional material (Costafreda et al., 2008). Emotional disturbance is at the core of depressive symptomatology, and cognitive disturbances interact with the affective tone of stimulus material. Thus, depressed patients show negative biases in attentional and memory processing and a tendency to interpret information negatively (Clark et al., 2009 for review). In recent years, there have been numerous neuroimaging studies focused on the function of the amygdala, and interconnected regions, in mediating these emotional processing disturbances.

Face emotion processing

Some brain imaging studies have found that depressed patients show greater amygdala response to emotional faces than controls (Sheline et al., 2001; Fu et al., 2004, 2008a; Surguladze et al., 2005), but others have failed to replicate this finding (Gotlib et al., 2005; Keedwell et al., 2005; Dannlowski et al., 2008; Lee et al., 2008) and one (Lawrence et al., 2004) reported reduced amygdala response. These studies also report group differences in a range of other brain areas including hippocampus, hippocampal gyrus, ACC, insula, fusiform gyrus, caudate, thalamus, ventral striatum and frontal, parietal and temporal regions. However, the exact regions reported for each emotion and the direction of the group differences vary. These inconsistencies may be attributable to differences in the paradigms used; for example some have used subliminal stimuli (Sheline et al., 2001; Dannlowski et al., 2008) while others have not. This highlights a possible role for standardised measures for exploring emotional function. As in non-emotional studies, differences in clinical characteristics may also influence findings; both severity of depression and medication status may be important variables.

Emotional words and pictures

Although faces are most widely used, there have also been studies using other emotional stimuli. Siegle et al. (2002, 2006, 2007) used self-referential emotionally valenced words and found that

amygdala response to negative words was both increased and sustained for significantly longer in depressed participants compared to controls. Kumari et al. (2003) used pictures and sentences paired to create either a positive, negative or neutral message. In response to negative stimuli, they found decreased ACC response in depressed patients. Decreased responses in left medial frontal gyrus/ACC and hippocampus were also observed for positive stimuli. Similarly, Mitterschiffthaler et al. (2003) used positive and neutral pictures with anhedonic depressed patients and found reduced medial orbitofrontal cortex (OFC) responses to positive pictures in depressed patients. Interestingly, depressed participants had greater response to positive pictures in lateral OFC, an area typically associated with negative emotion and punishment (O'Doherty et al., 2001; Kringelbach, 2005). These findings suggest that depressive anhedonia may be mediated by altered balances in normal emotional processing systems. Different symptom profiles may be associated with differential responses to emotional stimuli, suggesting once again that it is important to carefully characterise patient groups to understand differences between studies.

Emotional processing biases

An important dimension of depressive symptomatology is the biasing effect of emotional valence on cognitive performance: patients are biased towards processing negative information. Dannlowski et al. (2007) found that bilateral amygdala response to masked negative face emotions correlated positively with a bias towards judging faces more negatively, an effect not seen for happy faces. More explicitly, Hamilton and Gotlib (2008) examined the neural basis of negative memory biases in depression. They reported that depressed participants displayed greater right amygdala activity in response to negative (but not positive) emotional pictures that they subsequently remembered. Memory for the negative pictures was also enhanced, suggesting that amygdala hyperactivity at encoding could be a basis for negatively biased memory. However, findings in this area are inconsistent; Roberson-Nay et al. (2006) also reported greater left amygdala activation in response to subsequently-remembered emotional stimuli (faces), but this was seen for happy and neutral faces as well as negative ones.

Studies have also considered the neuronal basis of affective biases in the attentional domain. Mitterschiffthaler et al. (2008) used an emotional Stroop task and showed that behavioural bias towards negative stimuli in depressed participants was associated with enhanced ACC response. Similarly, Elliott et al. (2002) reported increased ACC response to sad targets in an affective go-no go task in depressed patients, but reduced response to happy targets; the exact opposite of the pattern observed in healthy controls. See **Figure 1**.

Sad distracters were associated with enhanced OFC response in patients, an effect attributed to a failure to inhibit instinctive bias towards sad information. Wang et al. (2008) also reported enhanced inferior frontal response associated with reduced ability to disengage from sad distracters. Similarly, Dichter et al. (2009) observed greater activation in depressed patients in a number of prefrontal regions, including inferior, and orbitofrontal gyri and ACC, in response to neutral targets embedded in sad compared to neutral contexts, suggesting that relatively more prefrontal brain activation was required to disengage from sad images to respond to the target events. Matthews et al. (2009) suggested that inhibitory control abnormalities in depression may not be confined to the affective domain, observing abnormal inferior frontal and ACC function during a non-affective inhibitory control paradigm. However, they nevertheless argued that these inhibitory control deficits may be important determinants of negative processing biases in depression.

Performance feedback

Another area where emotional biases contribute to cognitive function in depression is in a proposed abnormal response to negative performance feedback (Elliott et al., 1997b; Murphy et al., 2003). Taylor-Tavares et al. (2008) examined the neural basis of this effect. They found that compared to controls, depressed participants failed to deactivate the right amygdala in response to negative feedback. The amygdala deactivation seen in controls may be a defence mechanism to allow them to continue with the task without being adversely affected by failure, a mechanism which may be reduced in depression. Steele et al. (2007) reported an attenuation of the

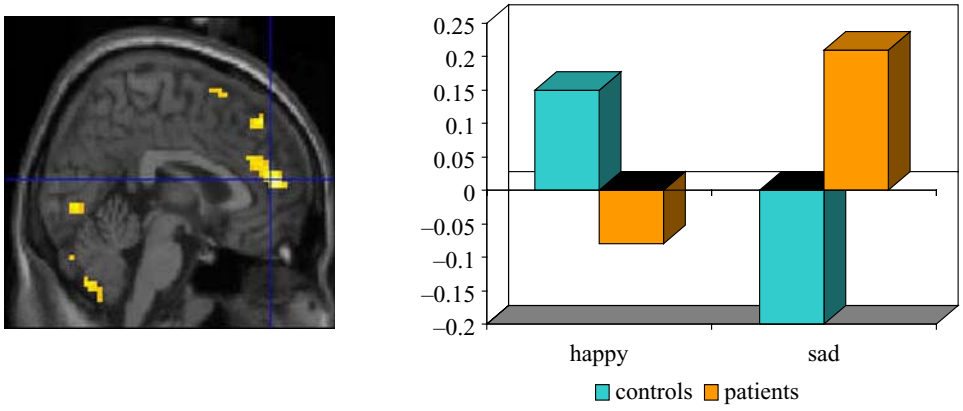


FIGURE 1 | Ventral ACC response to sad targets in depressed patients and happy targets in controls performing an affective go/nogo task. The left panel shows the focus of BOLD response and the right panel shows the adjusted BOLD response to happy and sad targets in patients and controls within this focus. Adapted from Elliott et al. (2002).

normal ACC response to negative feedback in depressed patients. The ACC is closely connected with the amygdala and these findings, combined with those of Taylor-Tavares et al. (2008), may suggest that response to negative feedback in depression is mediated by a dysfunctional balance between the emotional functions of the amygdala and the cognitive control functions of the ACC.

NETWORK MODELS OF DEPRESSION

The literature reviewed above highlights the complexity inherent in understanding the functional neuroanatomy of impaired cognition in depression, with various discrepancies and interpretational issues still unresolved. Further research in well-characterised samples will be needed to resolve these issues fully. However, some general trends emerge. Specifically, there is strong support for the theory that normally performing depressed patients show hyper-response within lateral frontal regions, while impaired performance is usually accompanied by hypo-response. These results are typically interpreted as representing inefficient cognitive processing within prefrontal regions. Negative emotional information is more salient to patients with depression compared to controls. Functional responses of limbic regions, particularly the amgydala, have been associated with biases observed in depressed patients towards negative information (faces, words, pictures, feedback). The ACC plays a role in both cognitive and emotional processing and the interface between them. Many activation studies in depression suggest abnormal ACC response but the nature of this abnormality (hypofunction vs. hyperfunction) varies widely depending on the cognitive challenge.

In general terms, disrupted cortico-limbic circuits, with a key modulating function for the ACC may explain both emotional biases and cognitive deficits in depression, as suggested in an influential model proposed by Mayberg (1997) and Mayberg et al. (1999). See **Figure 2**.

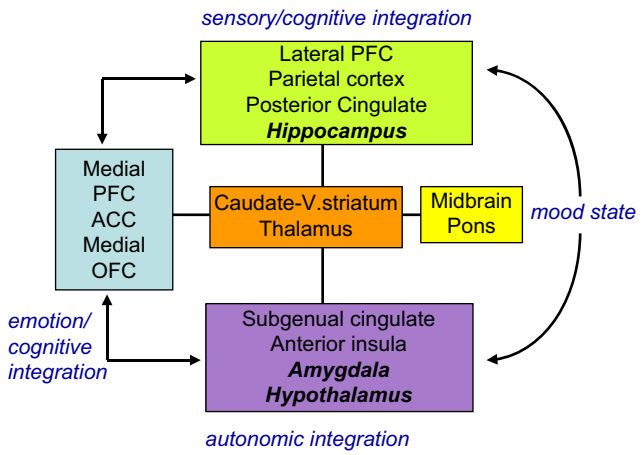


FIGURE 2 | Limbic-cortical dysregulation model. Interconnected regions are grouped into four 'compartments' relating to particular cognitive/behavioural functions. Within compartments there may be a segregation between areas (shown in plain and italic text) showing an inverse relationship on different imaging paradigms. These interactions are dysfunctional in depression and modulated by successful treatment. Adapted from Mayberg (1997) and Mayberg et al. (1999).

This model has been developed and refined in recent years and shown to have diagnostic value and a role in predicting treatment response (Mayberg, 2002, 2003). Network models of depression, directly generated from functional neuroimaging results, can be tested explicitly using new connectivity analysis techniques.

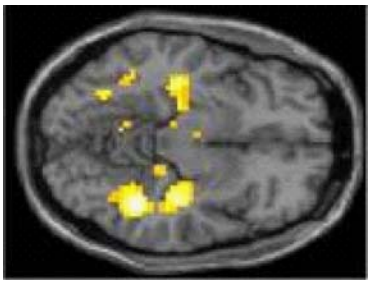
CONNECTIVITY ANALYSES

The consensus view holds that depression is mediated by disruptions within networks of interconnected brain regions, rather than depending on abnormal function within a particular region. While the results discussed above are certainly supportive of this view, more recent approaches have addressed connectivity directly. One approach is to explore the extent to which response in different brain regions is intercorrelated. For example, Hamilton and Gotlib (2008) demonstrated that right amygdala response to remembered negative pictures was more strongly correlated with ipsilateral hippocampus and caudate-putamen response in depressed subjects. A similar approach is to consider functional coupling between brain regions in response to particular cognitive challenges. Several studies have explored functional coupling of the amygdala and prefrontal regions (Johnstone et al., 2007; Siegle et al., 2007; Chen et al., 2008; Matthews et al., 2008). Matthews et al. (2008) reported reduced functional coupling of the amygdala and supragenual ACC during emotion processing associated with increasing severity of depression. Similarly, Chen et al. (2008) reported increased functional coupling of amygdala and ACC during face emotion processing following antidepressant treatment (i.e. as symptom severity was reduced). Siegle et al. (2007) observed that depressed patients showed enhanced amygdala response during emotional tasks, reduced DLPFC response during executive tasks and a decreased functional coupling between amygdala and DLPFC, highlighting the importance of the cognitive challenge in exploring connectivity.

A more comprehensive approach to connectivity is to use techniques such as structural equation modelling and dynamic causal modelling to explore changes in a pre-specified network of regions. Using this approach, Schlosser et al. (2008) assessed connectivity associated with a cognitive control task (Stroop) and observed enhanced task-related input from the dorsal to rostral ACC in subjects with depression, perhaps signalling a failure to downregulate rostral ACC function in an inhibitory control context. Recent unpublished work from our team (Goulden et al., 2009) suggests that there are also abnormalities when dynamic causal modelling is applied to remitted depressed patients performing a face processing task, as shown in **Figure 3**.

In the most explicit test of a disrupted connectivity model to date, Seminowicz et al. (2004) applied structural equation modelling in a path modelling meta-analysis. This approach tested the specificity and reliability of Mayberg's reciprocal connectivity model (**Figure 2**) across different studies. The approach suggested different patterns of disrupted connectivity in different subgroups of patients, in particular identifying differences between responders and non-responders to treatment. Thus for connectivity studies, as for regional response studies, it is important to fully characterise patient groups in order to compare different results.

The studies reviewed briefly in this section suggest that connectivity approaches to analysing functional imaging data from depressed patients represent an important step forward in understanding



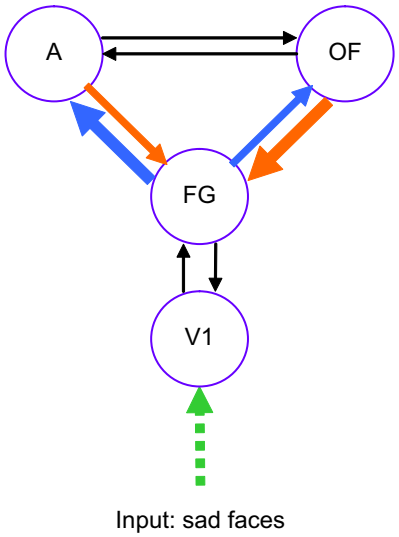


FIGURE 3 | Sad face processing in remitted depressed patients. The left panel shows attenuated bilateral hippocampus and fusiform signal in patients compared to controls. The right panel shows altered connectivity in patients obtained via dynamic causal modelling. The model tested was a right hemisphere model comprising primary visual cortex (V1), fusiform gyrus (FG), Amygdala (A) and orbitofrontal cortex (OFC). Connections shown in blue are stronger in patients (significant at $p < 0.05$ corrected for boldest arrow) while those in orange are weaker in patients (significant at $p < 0.05$ corrected for boldest arrow). Data acquired at the Wellcome Trust Clinical Research Facility, Manchester (Thomas et al., submitted; Goulden et al., 2009).

the disorder. Effective connectivity between limbic and prefrontal regions is disrupted in depression and the nature of this disruption depends on the cognitive challenge presented. The Seminowicz et al. (2004) study also emphasises that it is important to study different subgroups and to consider treatment response.

CLINICAL IMPLICATIONS OF COGNITIVE IMAGING

Many of the studies discussed in this review have suggested important relationships between clinical features and functional response to cognitive challenges. Some studies have reported correlations with severity; others have reported changes in response to treatment. Discrepancies between studies may also point to distinct functional response profiles in different subtypes of depression. While a detailed discussion of these issues is beyond our scope, we will highlight two areas that illustrate the potential of neuroimaging cognition to inform clinical approaches to depression.

REMITTED DEPRESSION STUDIES AS A MODEL FOR TRAIT EFFECTS

Studying the neuronal basis of cognitive function in remitted depression provides a model for considering which abnormalities may represent trait effects or vulnerability markers. Despite the growing literature highlighting persistent cognitive deficits and biases in remitted depression, few studies have investigated the neural correlates of these cognitive findings. In a cross-sectional study, Takami et al. (2007) found ACC activity to a verbal fluency task was attenuated in elderly remitted depressives who had experienced multiple previous episodes, though not in those who had experienced only a single episode. By contrast, Hugdahl et al. (2007) used a longitudinal design to show that with remission, inferior frontal gyrus and the superior and inferior parietal lobule activity to a mental arithmetic task normalized in recurrent depressive participants.

Subtle emotional biases may remain in remitted depression, even when behaviour has normalised, and functional imaging provides a method for assessing these biases. Liotti et al. (2002) demonstrated that induced sad mood in remitted patients, but not controls, was associated with decreased function in ventromedial prefrontal regions and anterior thalamus, while VLPFC showed increases. Gemar et al. (2007) found a similar pattern of results in unmedicated remitted participants, indicating that these results are not due to residual medication effects. Combining mood induction and cognitive challenge, Ramel et al. (2007) reported that amygdala response to negative words during induced sad mood predicted subsequent recall in remitted participants.

There is also neuroimaging evidence for persistent abnormalities in depression in the absence of an induced depressed mood. Neumeister et al. (2006) demonstrated enhanced amygdala activation and reduced ventral striatum activation in remitted participants viewing sad faces (compared to neutral). In a recent study we found remitted participants to have increased neural responses to happy faces and reduced response to sad and fearful faces, in contrast to the opposite pattern more commonly described in current depression. We suggest that this may represent a maintenance mechanism for remission with participants suppressing the negative emotional biases associated with depressed mood (Thomas et al., submitted).

Using remission as a model for trait vulnerability is not without interpretational problems. Most obviously, it is unclear whether abnormalities in remitted patients represent genuine vulnerability traits, or 'scarring' from prior depressed episodes. One approach to address this confound is to consider never-depressed patients who may be vulnerable to developing the disorder. For example, Chan et al. (2009) have reported enhanced response to fearful faces in highly neurotic subjects considered at risk for depression. Similarly,

Mannie et al. (2008) have reported impaired ACC response to emotional stimuli in young people with a strong family history of depression and therefore at risk themselves. However, these studies face the problem that relatively few of the subjects will go on to develop depression, and only long-term follow up can determine whether a specific pattern of response characterises these individuals. If imaging cognition could reliably identify individuals most vulnerable to depression, it may be possible to develop targeted intervention strategies for at-risk people that prevent development of depressive symptoms.

TREATMENT EFFECTS ON COGNITION

Serotonergic antidepressants have been associated with altered neuronal response to cognitive challenge in normal subjects. For example, Del-Ben et al. (2005) reported reduced limbic responses to negative faces after acute citalopram. Harmer et al. (2006) and Norbury et al. (2007) also reported reduced limbic response to negative faces after subacute doses of citalopram and reboxetine respectively. Similar findings have been reported in studies of antidepressant treatment in depressed patients. Studies have shown that participants who respond to treatment also have normalised (i.e. reduced) neural activity to emotional faces when retested (e.g. Sheline et al., 2001; Fu et al., 2004, 2007, 2008a). Neuronal correlates of response to psychological interventions have also been assessed (e.g. Roffman et al., 2005; Linden, 2006; Fu et al., 2008b). Changes are reported in the neuronal correlates of affective processing following cognitive behavioural therapy or interpersonal therapy. Thus, different forms of antidepressant therapy directly impact abnormal functional responses, particularly in the emotional domain.

Functional imaging of cognitive challenge has also proved a potential predictor of treatment response, which has important implications for clinical practice (Ressler and Mayberg, 2007). Fu et al. (2008b) and Davidson et al. (2003) have reported that subjects who showed greatest ACC response to negative emotional stimuli at baseline responded best to antidepressant treatment. Meanwhile, Siegle et al. (2006) found that subjects with low subgenual ACC response and high amygdala response to emotional stimuli responded best to cognitive behavioural therapy.

While considerable further research is needed to explore relationships between treatment response and cognitive imaging abnormalities, these studies suggest an exciting role for brain imaging measures in the development of new algorithms for diagnosis and management of depressed patients (Mayberg, 2007). It may be possible to identify cognitive neuroimaging biomarkers that can predict which patients are likely to respond to a particular intervention (or which intervention is most likely to work for a particular patient). It may also be possible to identify which patients are more likely to relapse after treatment.

FUTURE DIRECTIONS

In this review, we have discussed a number of inconsistencies in the literature on imaging cognition in depression. These discrepancies highlight a need for more comprehensive reporting in some imaging studies, in relation to both clinical features of the sample and characterisation of the cognitive challenges used. For example, medication status of patients, duration of illness, number of previous episodes and any co-morbidity may all contribute to differences between studies. Drawing comparisons between studies and explaining apparently conflicting results critically depends on clear characterisation of the patients studied. Similarly, it is important to carefully characterise controls and match them as closely as possible to the patient sample; for example, it is relatively common for academic researchers to recruit controls among university staff and students, who may not represent a typical population sample. Furthermore, it is important for studies to relate BOLD response as closely as possible to cognitive performance. Directly relating regional responses to performance levels and considering responses to correct and incorrect trials separately, for example, may allow for a clearer understanding of the relationship between neuronal function and cognition in this subtly affected patient group. Thus, future research in this area should report subject characteristics and relationships between BOLD response and performance as comprehensively as possible to facilitate cross-study comparisons.

Although our review has largely focused on BOLD contrast fMRI, other imaging modalities have also been used to study cognitive function in depression. For example, magnetoencephalograpy (MEG) and electroencephalography (EEG) have been used and provide greater temporal resolution than fMRI, which may be important in studying processes like emotional arousal or inhibition (McNeely et al., 2008; Moratti et al., 2008). It is also clear that combining this approach with fMRI may help explain some of the discrepancies in the literature. For example, Wacker et al. (2009) combined fMRI and resting EEG to assess responses in reward systems associated with anhedonia. This multimodal approach showed that anhedonia was associated with reduced response to reward (fMRI) but also increased resting state activity in the nucleus accumbens (EEG). These results suggest that multimodal imaging represents an important future research direction.

Our review also highlights theoretical directions for future research, to test specific hypotheses arising from the existing literature. As discussed above, there is something of a dearth of non-emotional cognitive imaging. Future studies are needed to explore the relationship between performance and prefrontal function, systematically varying task difficulty to determine whether this is a critical determinant of hyper- vs. hypo-frontality. Furthermore, there is a need for a fuller exploration of the neural correlates of memory dysfunction, given that this is one of the commonest cognitive symptoms reported by patients. Memory dysfunction is reported most frequently in elderly patients with depression, and functional imaging studies are needed to relate this structural pathology in the hippocampus and to compare memory problems in late life depression with those observed in other conditions (mild cognitive impairment or early Alzheimer's disease).

Although the neuronal basis of emotional abnormalities has been studied more widely, further research is needed to relate these abnormalities more closely to clinical symptoms. Many studies have used rather heterogeneous clinical samples and future studies could compare subtypes of patients with distinct patterns of symptoms and with distinct aetiological features. Longitudinal studies in this area will also be critical in understanding how emotional abnormalities relate to response to different treatments and long-term

prognosis. For both non-emotional and emotional cognitive neuroimaging, future research should exploit modern connectivity techniques to test network dysfunction hypotheses of depression.

Finally, brain imaging offers a powerful approach to exploring how genetic and environmental factors interact in conferring vulnerability and resilience to depression and large, systematic studies are needed in this area. As discussed above, this would provide the background for identifying neuroimaging biomarkers of both depression vulnerability and effective treatment, thus realising the potential of functional imaging in diagnosis and management.

CONCLUSIONS

In this review we have briefly summarised recent neuroimaging studies of non-emotional and emotional cognition in depression. These studies suggest that impaired executive function in depression is associated with inefficient cortical (and particularly lateral prefrontal) processing. Normal levels of performance can sometimes be achieved through recruitment of additional processing resources reflected in prefrontal hyperfunction. However, when normal performance cannot be achieved, prefrontal function is reduced. Emotional processing, particularly of negatively valenced material, is facilitated in depression and this is mediated by enhanced function of limbic regions, including the amygdala. The ACC plays a critical but complex role in depression, mediating the balance between limbic and cortical function in a context dependent manner. Models of cortico-limbic dysfunction (notably that of Mayberg, 1997; Mayberg et al., 1999) can explain this pattern of results, and modern connectivity techniques provide a means to test these models explicitly. Recent studies have started to identify the neurocognitive signature of vulnerability to depression and to assess and predict response to different treatment options. Neurocognitive assessment of depression using functional imaging therefore has exciting implications for diagnosis and treatment.

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