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Cingulate activity and fronto-temporal connectivity in people with prodromal signs of psychosis

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ABSTRACT

Schizophrenia is associated with fronto-temporal dysconnectivity, but it is not clear whether this is a risk factor for the disorder or is a consequence of the established illness. The aim of the present study was to use fMRI to investigate fronto-temporal connectivity in subjects with prodromal signs of schizophrenia using the Hayling Sentence Completion Task (HSCT). Thirty participants, 15 with an at risk mental state (ARMS) and 15 healthy controls were scanned whilst completing 80 sentence stems. The congruency and constraint of sentences varied across trials. Dynamic causal modelling (DCM) and Bayesian model selection (BMS) were used to compare alternative models of connectivity in a task related network. During the HSCT ARMS subjects did not differ from Healthy Controls in terms of fronto-temporal activation, i.e. there was neither a main effect of group nor a group-by-task interaction. However, there was both a significant main effect of group and a significant interaction in the anterior cingulate cortex (ACC), with greater ACC activity in the ARMS subjects. A systematic BMS procedure among 14 alternative DCMs including the ACC, middle frontal, and middle temporal gyri revealed intact task-dependent modulation of fronto-temporal effective connectivity in the ARMS group. However, ARMS subjects showed increased endogenous connection strength between the ACC and the middle temporal gyrus relative to healthy controls. Although task related fronto-temporal integration in the ARMS was intact, this may depend on increased engagement of the ACC which was not observed in healthy control subjects.

Introduction

Disordered brain connectivity is thought to be a central pathophysiological feature of schizophrenia (Walterfang et al., 2006; Stephan et al., 2009a, 2009b). Recently a number of functional imaging (Boksman et al., 2005; Ragland et al., 2001; Wolf et al., 2007; Yoon et al., 2008) and diffusion tensor imaging (DTI) studies (Hubl et al., 2004; Rosenberger et al., 2008; Shergill et al., 2007) have provided data consistent with this view. In particular, the disconnection hypothesis of schizophrenia was motivated by initial positron emission tomography (PET) studies showing abnormal patterns of functional connectivity between prefrontal and temporal lobe regions (Friston, 1998; Friston and Frith, 1995; Frith et al., 1995). Subsequent experimental evidence, using functional Magnetic Resonance Imaging (fMRI), has been largely consistent with this hypothesis, reporting altered fronto-temporal connectivity in schizophrenia patients relative to healthy control subjects (Fletcher et al., 1999; Frith et al., 1995; Lawrie et al., 2002; Winder et al., 2007). It is not clear, however, whether dysconnectivity contributes to the development of schizophrenia or whether it is a consequence of the illness or its treatment (Konrad and Winterer, 2008). A recent review of structural neuroimaging and electrophysiology studies in first episode schizophrenia concluded that there is evidence that connectivity is altered in the early stage of the disorder (Begre and Koenig, 2008). Other studies using electroencephalography (Winterer et al., 2003) and DTI (Konrad et al., 2009) suggest that fronto-temporal connectivity is perturbed in subjects at increased genetic risk of schizophrenia. Using functional magnetic resonance imaging (fMRI), Whalley et al. (2005) studied the relatives of patients with the Hayling Sentence Completion Task (HSCT; (Burgess and Shallice, 1996). They found functional dysconnectivity between cerebral cortical, thalamic, and cerebellar regions, but no evidence of fronto-temporal dysconnectivity. They suggested that the latter might be a feature of established schizophrenia but not of groups at high genetic risk of the disorder.

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Another approach is to study people at high risk as judged by clinical symptoms. Individuals with prodromal symptoms and signs of psychosis, such as attenuated psychotic symptoms and a decline in social and occupational function, are said to have an at risk mental state (ARMS), as these features are associated with a high risk of psychosis (Hafner, 2002; Yung et al., 1998). The ARMS is associated with abnormalities of regional brain function and structure that are often qualitatively similar to those seen in schizophrenia, but less marked (Fusar-Poli et al., 2007). Volumetric MRI studies have identified reductions in grey matter volume in prefrontal and temporal regions (Borgwardt et al., 2007; Meisenzahl et al., 2008; Pantelis et al., 2003) and fMRI studies have reported altered activation in frontal regions during tasks of executive functions and working memory (Broome et al., 2009; Morey et al., 2005). The aim of the present study was to use fMRI to investigate fronto-temporal connectivity in the ARMS. We used the HSCT, which requires participants to complete a sentence with a semantically related congruent word (response Initiation) or an unrelated incongruent word (response Suppression). We selected this task for two reasons. Firstly, performance of the HSCT is normally associated with robust engagement of the prefrontal and lateral temporal cortex. Secondly, we have recently shown that when healthy controls perform the HSCT effective connectivity between frontal and temporal regions is greater during response Suppression relative to Initiation (Allen et al., 2008). In the present study we used dynamic causal modelling (DCM) (Friston et al., 2003), a recently developed method to infer effective connectivity and its modulation by specific experimental contexts (e.g. task demands) from fMRI measurements.

We first tested the hypothesis that during the HSCT, ARMS subjects would show an altered pattern of frontal and temporal activation relative to healthy controls particularly during response Suppression, the most cognitively demanding of the task conditions. Using DCM, we then tested the hypothesis that task-dependent effective connectivity between frontal and temporal regions would be diminished in ARMS subjects compared to healthy controls.

Materials and methods

Participants

Thirty subjects (15 healthy controls and 15 with an ARMS) participated in the study. Results for the healthy controls have been previously reported by us (Allen et al. 2008). All were right-handed, spoke English as their first language, and had no history of neurological illness, drug, or alcohol dependence. The study had National Health Service UK Research Ethics Committee (CoREC) approval and all participants gave informed consent. FMRI data from both healthy controls and ARMS subjects were collected over the same time period. All participants had an estimated premorbid IQ in the normal range as assessed using the Wide Range Achievement Test —Revised (WRAT) (Jastak and Wilkinson, 1984). Exclusion criteria were a history of past or present psychiatric illness, significant head trauma or any CNS disease, current medical illness, and use of any regular medication in the last 2 months. No subjects had a significant history of drug or alcohol use. Any participants reporting excessive use of alcohol or recent recreational drug use (use of cannabis, stimulants, hallucinogens, or opiates in the 2 weeks prior to the fMRI scan) were also excluded.

Healthy controls

Fifteen healthy, right-handed male ($n=8$) and female volunteers ($n=7$) were recruited from the same geographical area as the ARMS group via advertisements and matched to the ARMS group in terms of age, years of education, and premorbid IQ (Table 1). Their self-reported ethnicity was white British ($n=10$), black ($n=3$), and mixed ($n=2$).

Table 1
Mean and standard deviations for demographic characteristics and symptom ratings.

	Healthy controls ($n=15$)	ARMS ($n=15$)	Analysis
Age (years)	25.75 (4.95)	26.85 (4.95)	$t=1.23$; $p=0.21$
Gender	8M: 7F	9M: 6F	$\chi^2=0.05$; $p=0.81$
WRAT estimated premorbid IQ	105 (15.47)	103 (15.66)	$t=0.36$; $p=0.75$
Years of education	14.89 (3.11)	13.76 (2.87)	$t=0.1.56$; $p=0.18$
Symptoms			
PANSS total		47 (13)	
PANSS positive		11 (4)	
PANSS negative		11 (4)	
PANSS general		24 (7)	

Subjects with an At Risk Mental State (ARMS)

Fifteen right-handed males ($n=9$) and females ($n=6$) participated. Mean age, years of education, and estimated premorbid IQ are shown in Table 1. Their self-reported ethnicity was white British ($n=9$), black ($n=2$), and mixed ($n=4$). ARMS subjects were recruited via OASIS (Outreach and Support in South London), a clinical service for people at high risk of developing psychosis (Broome et al., 2005). The ARMS was defined according to the Personal Assessment and Crisis Evaluation (PACE) criteria (Yung et al., 1998) and the diagnosis was made via a detailed clinical assessment using the Comprehensive Assessment of At Risk Mental States (Phillips et al., 2000). Subjects met one or more of the following criteria, namely, a) attenuated psychotic symptoms, b) brief limited intermittent psychosis, or c) a recent decline in function, together with either schizotypal personality disorder or a first degree relative with a psychotic disorder. All ARMS subjects were experiencing attenuated psychotic symptoms, four had also experienced a brief limited intermittent psychosis, and three had a family history together with a decline in function. The mean Global Assessment of Functioning score of the group at clinical presentation was 61. Psychopathology on the day of scanning was assessed using the Positive and Negative Symptom Scales (PANSS) (Kay, 1990). The PANSS symptom ratings are presented in Table 1. Subjects were scanned shortly after clinical presentation (mean duration between presentation and MRI scanning = 36.61 days). Two ARMS subjects had received low doses of risperidone and quetiapine at the time of scanning. All the other subjects were naïve to antipsychotic and other forms of psychotropic medication. The subjects will be monitored to determine their long term clinical outcome; this process is ongoing.

FMRI task design

The Hayling Sentence Completion Task (Burgess and Shallice, 1996) was adapted for use in a functional MRI experiment. Eighty sentence stems were selected from those created by Bloom and Fischler (1980) and Arcuri et al. (2001). The stems comprised either six or seven words and were selected on the basis of being associated with either a high (>0.9) or a low (<0.5) Cloze probability (CP). This is the probability that a particular word will be used to complete a given sentence (Kutas and Hillyard, 1984). The sentences were then assigned to either a response Initiation condition, in which participants were required to complete the sentence with a congruent response (i.e. He posted the letter without a “STAMP”), or a response Suppression condition, in which a non-congruent completion was required (i.e. The boy went to an expensive “GIRAFFE”). This yielded a factorial design, with congruency (Initiation and Suppression) and constraint (low CP and high CP) as factors. The forty sentence stems in each of the congruency conditions were arranged into blocks containing five stems each. Sentence stems were presented visually one at a time. The experimental conditions were contrasted with a control condition which consisted of overt articulation of the word ‘REST’ presented visually every 4 seconds after a fixation cross also