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Failure to deactivate medial prefrontal cortex in people at high risk for psychosis

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ABSTRACT

Impaired working memory is a core feature of schizophrenia and is linked with altered engagement the lateral prefrontal cortex. Although altered PFC activation has been reported in people with increased risk of psychosis, at present it is not clear if this neurofunctional alteration differs between familial and clinical risk states and/or increases in line with the level of psychosis risk. We addressed this issue by using functional MRI and a working memory paradigm to study familial and clinical high-risk groups. We recruited 17 subjects at ultra-high-risk (UHR) for psychosis, 10 non-affected siblings of patients with schizophrenia (familial high risk [FHR]) and 15 healthy controls. Subjects were scanned while performing the N-back working memory task. There was a relationship between the level of task-related deactivation in the medial PFC and precuneus and the level of psychosis risk, with deactivation weakest in the UHR group, greatest in healthy controls, and at an intermediate level in the FHR group. In the high-risk groups, activation in the precuneus was associated with the level of negative symptoms. These data suggest that increased vulnerability to psychosis is associated with a failure to deactivate in the medial PFC and precuneus during a working memory task, and appears to be most evident in subjects at clinical, as opposed to familial high risk.

1. Introduction

Impaired working memory (WM) is a robust feature of schizophrenia and is thought to reflect prefrontal cortex (PFC) dysfunction [27]. Although much attention has been devoted to altered engagement of the lateral PFC, presenting as both hypo- and hyperfrontality [15], the disorder is also associated with a failure to deactivate the medial PFC (mPFC) during task performance. The latter is thought to be associated with a dysfunction of the default mode network (DMN) [17], a network of brain regions that are active during a rest or baseline condition and usually deactivate during engagement in a cognitive tasks [5]. PFC dysfunction has also been reported in people at familial high-risk for schizophrenia (FHR) [39] and in people at clinical or ultra-high-risk (UHR; individuals who present with attenuated psychotic symptoms and/or a decline in function) for psychosis [1,4,28]. However, it is not clear to what extent PFC dysfunction reflects varying levels of psychosis risk mediated via genetic, non-genetic or illness-related (e.g. symptoms, medication) factors. Moreover, while both FHR and UHR individuals have an increased vulnerability to psychosis compared to the general population, the risk of subsequently developing the disorder is substantially greater in the UHR cohorts (approximately 30% over the next two years [13], compared to 6–13% over their lifetime in FHR cohorts [16,29]).

Whether mPFC dysfunction increases with the level of psychosis risk is not clear. The aim of the present study was to use functional magnetic resonance imaging (fMRI) to explore PFC (dys-)function in relation to different levels of psychosis risk, independent of the manifestation of the disorder. We measured PFC activation during a working memory task in subjects at UHR for psychosis, FHR subjects and healthy control subjects. We first tested the hypothesis that PFC dysfunction would be evident in all people at risk of psychosis (i.e. FHR and UHR groups). We then

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explored whether PFC dysfunction increased in line with psychosis risk by comparing FHR and UHR groups.

2. Methods

2.1. Participants

The study was approved by the local research ethics committee and was conducted in accordance with the Declaration of Helsinki [41]. All participants gave written informed consent. The sample consisted of 17 ultra-high-risk subjects (UHR), 10 subjects with a familial high-risk for psychosis (non-affected siblings of patients with schizophrenia; FHR) and 15 healthy control subjects (CTRL) without any personal or family history of psychiatric disorders. UHR and CTRL samples have previously been reported by Broome et al. [4]. FHR participants were recruited as part of the Maudsley Family Study [23] but fMRI data (N-back task) from this group has not been used in any previous studies. All participants were right-handed [7] and native speakers of English. Demographic and clinical details (Positive and Negative Symptoms Scales; PANSS [21]) and IQ estimates (assessed using the National Adult Reading Test; NART [30]) are provided in Table 1.

2.1.1. Ultra-high-risk group (UHR)

Subjects meeting the following criteria for the UHR state of psychosis [42] were recruited from Outreach and Support in South London (OASIS) [3]: age between 18 and 35 years, help-seeking, meet the criteria for one or more of the following three groups: group 1: attenuated psychotic symptoms (APS), group 2: brief limited intermittent psychotic symptoms (BLIPS; a history of one or more episodes of frank psychotic symptoms resolving spontaneously within 1 week in the past year), group (3) a recent decline in function, together with either the presence of schizotypal personality disorder or a family history of psychosis in a first-degree relative. The diagnosis was based on assessment by two experienced clinicians using the Comprehensive Assessment for the At Risk Mental State [43] and a consensus meeting with the clinical team. All UHR subjects met APS criteria, 3 subjects met both APS and BLIPS criteria and 1 subject met APS criteria and also had a family history of psychosis. UHR subjects' mean Global Assessment of Functioning scores (GAF) [19] was 57.5 (±12.1, range: 35–75). All subjects were drug-naive at the time of scanning. The subjects were representative of the local population of people presenting with an UHR state of psychosis in terms of age, gender, ethnicity, duration and intensity of symptoms [3]. Over the 2-year follow-up period at the OASIS clinic, 3 of the UHR subjects (18%) developed frank psychosis.

2.1.2. Familial high-risk group (FHR)

Subjects in this group were non-affected, non-help-seeking siblings of multiply affected patients with schizophrenia, who participated in the Maudsley Family Study [23]. Subjects were from families in which the index patient had at least one first- or second-degree relative affected with schizophrenia, another non-organic psychotic disorder, or schizotypal disorder. Apart from their affected sibling, the FHR subjects thus had at least one other first- or second-degree relative with a psychotic disorder, indicating a relatively high putative genetic load. The subjects were recruited through voluntary support groups or by direct referral by the affected sibling's consultant psychiatrist. Additionally, recruitment advertisements were placed in the newsletters of national and international schizophrenia support groups. Structured diagnostic interviews were performed to enable DSM-IV diagnoses (see [23] for details). Of the 10 unaffected relatives of schizophrenia patients, 5 relatives fulfilled criteria for lifetime DSM-IV axis 1 disorder, 3 for major depressive disorder (DSM-IV: 296.20–296.30) and 2 for anxiety and panic disorders (DSM-IV: 300.01). None of the FHR group met criteria for any schizophrenia spectrum disorder or had experienced a recent decline in functioning. One FHR subject was taking an antidepressant (amitryptiline 50 mg/day), all other FHR subjects were medication free.

Table 1
Demographic and psychopathological characteristics.

	UHR ($n=17$)	FHR ($n=10$)	Controls ($n=15$)	Statistic
Age				
Mean (SD)	24.3 (4.2)	40.3 (10.7)	25.6 (4.8)	$F(2, 39)=21.6$[a]
Range	20–34	29–59	19–35	
IQ				
Mean (SD)	101.7 (11.7)	111.9 (7.5)	123.2 (16.2)	$F(2, 39)=15.7$[a]
Range	95.5–108.0	105.0–118.8	110.7–135.7	
Gender (n, female)	5	5	5	$X^2(2)=1.2$ (n.s.)
Ethnicity (%)				
White	76.5	100	66.7	$X^2(6)=8.7$ (n.s.)
Black	11.8	0	26.7	
Oriental	11.8	0	0	
Mixed	0	0	0	
Other	0	0	6.7	
PANSS score (mean, SD)				
Positive	11.8 (3.3)	10.9 (9.9)		$F(1,23)=0.1$ (n.s.)
Negative	11.6 (5.0)	7.2 (0.7)		$F(1,23)=6.5$[b]
General	25.3 (7.7)	17.2 (5.3)		$F(1,23)=7.7$[b]
CAARMS score (mean, SD)				
Disorders of thought content	5.9 (6.3)			
Range	2–23			
Perceptual abnormalities	2.2 (1.5)			
Range	0–4			
Disorganized speech	2.1 (1.5)			
Range	0–4			

[a] $P \leq 0.001$.
[b] $P < 0.05$.