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Elucidating neuroanatomical alterations in the at risk mental state and first episode psychosis: A combined voxel-based morphometry and voxel-based cortical thickness study ☆

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ABSTRACT

Previous studies have reported alterations in grey matter volume and cortical thickness in individuals at high risk of developing psychosis and patients in the early stages of the disorder. Because these studies have typically focused on either grey matter volume or cortical thickness separately, the relationship between these two types of alterations is currently unclear. In the present investigation we used both voxel-based cortical thickness (VBCT) and voxel-based morphometry (VBM) to examine neuroanatomical differences in 21 individuals with an At Risk Mental State (ARMS) for psychosis, 26 patients with a First Episode of Psychosis (FEP) and 24 healthy controls. Statistical inferences were made at $P < 0.05$ after correction for multiple comparisons. Cortical thinning in the right superior temporal gyrus was observed in both individuals at high risk of developing psychosis and patients with a first episode of the disorder, and therefore is likely to represent a marker of vulnerability. In contrast, the right posterior cingulate cortex showed cortical thinning in FEP patients relative to individuals at high risk, and therefore appears to be implicated in the onset of the disease. These neuroanatomical differences were expressed in terms of cortical thickness but not in terms of grey matter volume, and therefore may reflect specific cortical atrophy as opposed to variations in sulcal and gyral morphology.

1. Introduction

There is increasing interest in the investigation of neuroanatomical alterations in clinically healthy individuals at high risk for psychosis and patients in the early stages of the disorder, in order to develop potential biomarkers for early diagnosis. The vast majority of the studies have examined neuroanatomical alterations by measuring grey matter volume (GMV) using voxel-based morphometry (VBM) (Kubicki et al., 2002; Pantelis et al., 2003; Narr et al., 2005; Borgwardt et al., 2007b; Borgwardt et al., 2008; Meisenzahl et al., 2008; Witthaus et al., 2009; Mechelli et al., 2011); in addition, a smaller number of studies have measured cortical thickness(CT) using a cortical surface-based approach (Wiegand et al., 2004; Fornito et al., 2008; Schultz et al., 2010; Ziermans et al., 2010; Jung et al., 2011). With regard to patients in the early stages of psychosis, consistent GMV and CT alterations have been reported in medial and lateral temporal regions and, to a lesser extent, dorsolateral prefrontal and cingulate regions (Kubicki et al., 2002; Wiegand et al., 2004; Narr et al., 2005; Fornito et al., 2008; Witthaus et al., 2009; Schultz et al., 2010; Bodnar et al., 2011; Jung et al., 2011).With regard to individuals at high risk of developing the disorder, GVM and CT alterations have been reported in frontal, cingulate and temporal regions (Borgwardt et al., 2007b; Witthaus et al., 2009; Ziermans et al., 2010; Jung et al., 2011).

The studies published so far have typically focused on either grey matter volume or cortical thickness separately; however these two measurements reflect complementary aspects of neuroanatomy and may provide different sensitivity depending on the pathophysiological process under investigation. More specifically, the analysis of cortical thickness targets the presence of specific cortical atrophy, whereas the analysis of grey matter volume returns a mixed measure which depends on local cortical thickness as well as cortical folding and gyrification (i.e. cortical surface area) (Hutton et al., 2008). Thus, when used in combination, GMV and CT measurements provide more comprehensive information about the underlying pathophysiological changes.

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At present, only two studies have examined both GMV and CT in the early phases of psychosis (Voets et al., 2008; Takayanagi et al., 2011); these have reported discrepant findings as to whether GMV and CT alterations are expressed in similar or different areas. More specifically, Takayanagi et al. (2011) observed reduced CT and GMV in prefrontal and temporal regions in patients with a first episode of psychosis (Takayanagi et al., 2011). In contrast, Voets and colleagues showed widespread but focally distinct patterns of CT and GMV alterations in adolescents with early-onset schizophrenia (Voets et al., 2008). Moreover, to the best of our knowledge, no previous study has examined both aspects of neuroanatomy in both patients with a first episode of psychosis (FEP) and individuals at high risk of developing the disorder.

In the present study we therefore employed both voxel-based CT (VBCT; Hutton et al., 2008) and voxel-based morphometry (VBM; Ashburner and Friston, 2000) to investigate neuroanatomical alterations in patients with a first episode of psychosis (FEP) and individuals with an at risk mental state (ARMS) for psychosis relative to healthy controls. These two analytical techniques were chosen because they use the same pre-processing and registration procedures and allow the identification of voxel-level GMV and CT alterations within the same volumetric space, thereby minimizing any potential confounding methodological differences (Hutton et al., 2009; Nagy et al., 2011). Our main aim was to examine whether GMV and CT alterations precede the clinical manifestation of psychosis and therefore represent neuroanatomical markers of vulnerability to this disorder. We hypothesized that (1) both individuals with an ARMS and FEP patients would present with common cortical alterations in a network of interest comprising frontal, temporal and cingulate regions and (2) FEP patients would show more pronounced alterations compared to ARMS individuals in these regions. Our secondary aim was to examine whether VBM and VBCT would reveal distinct or similar alterations within our network of interest. We expected that the two techniques would reveal focally distinct GMV and CT effects, reflecting different underlying pathophysiological processes.

2. Methods

2.1. Participants

The study was approved by the local Research Ethics Committee. Participants gave written informed consent after a full description of the aims and design of the study. The following exclusion criteria applied to all participants: (i) a history of neurological disorders; (ii) head trauma resulting in loss of consciousness for over 1 h; (iii) evidence of substance abuse and dependence disorder according to the DSM-IV criteria and (iv) suspected or confirmed pregnancy. All but one subject in each group were right-handed, while English was the first and native language of all the participants in this study.

2.1.1. First episode psychosis (FEP) group

Twenty-six subjects were recruited from early intervention services within the South London and Maudsley National Health Trust. All individuals presented for the first time to the local psychiatric services and met ICD-10 criteria schizophreniform psychosis (WHO, 1992). One patient only was medication naive while the remaining had been treated for a mean of 155 days at chlorpromazine equivalent mean dose of 242 mg/day. See Table 1 for the demographic characteristics of this sample.

Table 1
Demographic and clinical characteristics of the 70 participants.

	Healthy controls ($n = 23$)	At risk mental state ($n = 21$)	First episode psychosis ($n = 26$)	Statistics
Age (s.d.)	24.2 (4.2)	22.14 (3.3)[a]	26.08 (5.63)[a]	$F = 4.227 p = 0.019$
Male/female	12 M:11 F	9 M:12 F	18 M:8 F	$\chi^2 = 2.60$, n.s.
Premorbid IQ (s.d.)	108.8 (10.13)	101.5 (13.5)	101.81 (11.2)	$F = 2.924\ p = 0.06$
Antipsychotic medication	23 N	2 M:19 N	24 M:2 N[b]	$\chi^2 = 54.32\ p = 0.001$
Total intracranial volume cm^3 (s.d.)	1537 (187)	1538(190)	1520(148)	$F = 0.78$, n.s.
Psychophatology scores, mean (s.d.)				
PANSS total	NA	52.57 (9.0)	54.69 (14.5)	$t = -0.55$, n.s.
PANSS positive	NA	12.89 (3.6)	13.42 (5.2)	$t = -0.378$, n.s
PANSS negative	NA	14 (4.08)	13.96 (4.9)	$t = 0.028$, n.s.
PANSS hallucinations	NA	2.73 (1.3)	1.92 (1.23)	$t = 2.09\ p = 0.043$
PANSS delusions	NA	2.68 (1.62)	3.00 (1.62)	$t = -0.723$, n.s.
CAARMS total	NA	39.47(15.63)	NA	
CAARMS intake criteria for ARMS				
Global functioning and trait markers, No. (%) of subjects		2 (9.5)		
Attenuated psychotic symptoms, No. (%)		19 (90.5)		
Brief limited intermittent psychotic symptoms, No. (%)		2 (9.5)		
Clinical outcome for ARMS (24 months)				
Individuals with finished follow-up, No. (%)		9 (42.8)		
With transition, No. (%)		0		
Without transition, No. (%)		9(42.8)		
Drops-out/Unfinished follow-up, No. (%)		12(57.2)		
Clinical outcome for FEP (12 months)				
Schizophrenia/ongoing psychosis, No.			12 (46.1)	
Remission/stable mental state, No.			13 (50)	
Schizoaffective disorder, No.			0	
Mood disorder, No.			0	
Drops-out, No.			1 (3.9)	

Abbreviations: PANSS, Positive and Negative Syndrome Scale; CAARMS, Comprehensive Assessment of At Risk Mental State; No., number.
[a] ARMS versus FEP.
[b] Healthy controls versus FEP.