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Correlated structural and functional brain abnormalities in the default mode network in schizophrenia patients

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ABSTRACT

Background: There is increasing evidence of default mode network (DMN) dysfunction in schizophrenia. It has also been suggested that brain structural changes are maximal in a medial frontal area which overlaps with the anterior midline node of this network.
Methods: Brain deactivations were examined in 14 schizophrenic patients and 14 controls during performance of two tasks requiring identification or labelling of facial emotions. Grey matter and white matter volumes were compared using voxel-based morphometry.
Results: Relative to the controls, the schizophrenic patients showed failure to deactivate in the anterior and posterior midline nodes of the default mode network, as well as other areas considered to be part of the network. Grey matter volume reductions in the patients were found in medial cortical regions which overlapped with the same parts of the network. The functional and structural changes showed significant correlations in a number of medial cortical areas.
Conclusions: Failure of deactivation in the default mode network is seen in schizophrenic patients when they perform facial emotion tasks. This failure is more extensive than that seen during performance of working memory tasks. The study also supports recent findings of brain structural changes in schizophrenia in the territory of the default mode network.

1. Introduction

Studies over the last ten years have documented the existence of the so-called default mode network (DMN), a system of brain regions that are active at rest or during passive viewing of stimuli, but which deactivate during performance of a wide range of cognitive tasks (Gusnard and Raichle, 2001; Raichle et al., 2001; Buckner et al., 2008). Important components of this network are two midline cortical regions, the medial prefrontal cortex anteriorly, including but not limited to the anterior cingulate gyrus, and the precuneus/posterior cingulate cortex posteriorly. Because the reduction in activity takes place when subjects perform active goal-oriented tasks, it is widely suspected that the DMN interacts reciprocally with other networks involved in task performance (Buckner et al., 2008; Fox et al., 2005). Beyond this, the DMN is believed to play a role in self-directed mentation such as recall of personal experiences, making social and emotional judgements, envisioning the future and being involved in theory of mind (Buckner et al., 2008; Gusnard, 2005).

DMN dysfunction has been reported in schizophrenia, although the findings have been complex. Harrison et al. (2007) found that schizophrenic patients showed greater deactivation than controls in the anterior and posterior midline nodes of the DMN during a task requiring response suppression. In contrast, other authors have reported a failure of deactivation

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during performance of the Sternberg working memory task (Kim et al., 2009) and the n-back task (Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009). A mixed pattern of abnormality has also been reported, with schizophrenic patients showing greater deactivation in the medial frontal cortex and parahippocampal gyrus, but a failure of deactivation in the precuneus and posterior cingulate cortex during an auditory oddball task (Garrity et al., 2007).

Two recent studies have found evidence of structural abnormalities associated with dysfunctional regions in the DMN. Camchong et al. (2009) identified functional connectivity abnormality in the anterior node of the DMN, plus reduced fractional anisotropy (FA) on diffusion tensor imaging (DTI) in the white matter subjacent to this area. Pomarol-Clotet et al. (2010) found that grey matter volume reductions in a group of chronic schizophrenic patients predominated in the medial frontal cortex, where they overlapped substantially with the area where failure of deactivation was found during performance of the n-back task. Additionally, DTI combined with tractography revealed abnormality in an area of the anterior corpus callosum whose fibres again projected to the medial frontal cortex.

These studies implicate the DMN in schizophrenia, but unanswered questions remain. One obvious problem is that it has not been established if the functional imaging abnormality takes the form of increased task-related deactivation or failure of deactivation. Secondly, it is not clear whether the whole of the default mode network is affected or just the anterior 'hub' in the medial frontal cortex, which might be dysfunctional in schizophrenia for other reasons, for example the presence of intrinsic frontal lobe pathology. Thirdly, there are issues about the nature of the tasks used: most studies to date have used working memory tasks (Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009), or other executive tasks like response suppression (Harrison et al., 2007) or tasks which make demands on prefrontal cortex function (Garrity et al., 2007). However, default mode dysfunction implies that the failure to deactivate should be seen across a wide range of cognitive tasks, not just those with a clear frontal/executive component. Finally, claims that DMN functional abnormality might be associated with structural brain change in schizophrenia require further corroboration.

In this study we a) examined patterns of brain deactivation in schizophrenic patients using two non-executive tasks; and b) investigated whether the changes in the pattern of deactivation in the disorder were related to structural abnormality. We did this by means of a re-analysis of data from a previous study which used two cognitive-demanding emotional tasks involving identification of emotions from facial expressions.

2. Materials and methods

2.1. Participants

Fourteen right-handed patients with a DSM-IV diagnosis of schizophrenia were recruited from the psychiatry department of Sainte Marguerite Hospital (Marseille). All patients were in stable clinical condition at the time of testing. Most were taking atypical antipsychotics (amisulpride 3, risperidone 3, olanzapine 3 and aripiprazole 2) but three were taking haloperidol. Demographic and clinical details are shown in Table 1.

Table 1
Clinical and demographic characteristics of patients and control.

	Healthy controls	Schizophrenic patients
	n = 14	n = 14
Age (years, SD)	34.6 (6)	37.3 (8.9)
Age range	23–48	22–56
Gender (male/female)	9/5	9/5
Education level (years, SD)	14.2 (2.1)	12.2 (4.2)
Parent's education level (years, SD)	12 .2(3.3)	13.1 (4.4)
Duration of illness (years, SD)		14 (6.7)
Total PANSS score (mean, SD)		60.7 (12.0)
Negative factor (mean, SD)		13.1 (5.5)
Positive factor (mean, SD)		24.7 (8.4)
Excitation factor (mean, SD)		8.4 (2.5)
Cognitive factor (mean, SD)		7.9 (3.3)
Depression factor (mean, SD)		6.5 (2.7)

The controls were 14 healthy subjects matched to the patients for handedness, age, educational level and parental educational level. They had no history of psychiatric or neurological disease and no history of drug abuse.

The study was approved by the local ethics committee (CCPPRB, Marseille). Each participant was registered on the French National File and gave written informed consent before entering the study.

2.2. Procedure

The fMRI paradigm has been described in detail elsewhere (Fakra et al., 2008). Briefly, it consisted of two tasks using human faces depicting anger or fear. In the *matching* condition, subjects viewed a target face and had to select which one of two other faces presented on the same screen expressed the same emotion as the target face. In the *labelling* condition, subjects viewed the same target face but had to judge which of two verbal labels, angry or afraid, best described the emotion. As a control task, subjects viewed a target oval shape and had to choose which of two ovals matched it (see Fig. 1).

2.3. Neuroimaging data acquisition

Data acquisition was performed on a 3-T MEDSPEC 30/80 AVANCE imager (Bruker, Germany). Functional scans were acquired using a T2*-weighted gradient-echoplanar sequence (TR/TE = 3000/35 ms; FOV = 19.2 × 19.2 cm, 64 × 64 matrix; flip angle = 90°). 36 axial slices were obtained with a contiguous slice thickness of 3 mm.

The functional paradigm consisted of two consecutive sessions of 12 blocks, three blocks of 44.5 s each of matching or labelling facial emotion interleaved with six control blocks of 22 s duration (inter-block = 2 s). Images were presented for 4 s with an inter-stimulus interval of 0.5 s. The paradigm was counterbalanced across subjects.

Following the functional scans, a set of high-resolution T1-weighted images was acquired (TE/TR = 5/25 ms, TI = 800 ms, flip angle = 15°, matrix = 256 × 256 × 128).