Task-induced deactivation of midline cortical regions in schizophrenia assessed with fMRI

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Abstract

Task-induced deactivations (TIDs) of midline cortical regions are readily observed in fMRI studies and may reflect elements of a ‘default-mode’ of brain function associated with self-directed mental processes at rest. In this study, we examined this TID phenomenon in schizophrenia and its relevance to patients’ symptoms, task performance and level of emotional awareness. Relative to control subjects, patients showed significantly greater TID of the rostral anterior cingulate (rAC)/medial prefrontal cortex (mPFC) and precuneus (PrC)/posterior cingulate cortex (PC). The magnitude of prefrontal TIDs was associated with patients’ task performance and emotional awareness for others. The nature of these associations suggests a complex interchange between cognitive and emotional influences on the resting-state activity of these prefrontal ‘default mode’ regions in schizophrenia.

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1. Introduction

Schizophrenia is characterized by marked disturbances of insight (Shad et al., 2006), a multifactorial behavioral construct involving aspects of self-awareness, emotion and introspection (Marks et al., 2000; Medalia and Lim, 2004). Recent functional magnetic resonance imaging (fMRI) studies suggest that a midline cortical network, including the medial prefrontal cortex (mPFC), adjacent rostral anterior cingulate (rAC), posterior cingulate (PC) and precuneus (PrC), may be relevant to understanding the neural basis of such mental processes (Gusnard et al., 2001b; Raichle et al., 2001). In this context, these midline regions show a characteristically high metabolic rate at rest that is suppressed, or ‘deactivated’, when attention is engaged in a cognitive task (Gusnard et al., 2001b; Raichle et al., 2001). These task-induced deactivations (TIDs) are thought to reflect elements of an intrinsic or ‘default-mode’ of brain function associated with self-directed mental processes during rest (Greicius and Menon, 2004; Gusnard et al., 2001a; Northoff et al., 2006; Raichle et al., 2001). In this study, we examined whether this midline TID phenomenon is altered in schizophrenia and related to patients’ symptoms, level of emotional awareness and cognitive task performance.
2. Methods and materials

2.1. Subjects

Twelve male schizophrenia patients and fourteen male control subjects were included in this study. Patients were selected from original sample of fourteen who completed the fMRI session. Two patients were excluded due to abrupt head movements (both >6 mm) in the last resting block. No subject had a history of major medical or neurological illness, and no control subject had a history of psychiatric illness using the Structured Clinical Interview for DSM-IV Disorders (First et al., 1998). All patients had a well-established illness and were stable outpatients fulfilling criteria for a current Axis-I diagnoses of schizophrenia (First et al., 1998). Patients’ symptom scores (Kay et al., 1991) were; total =58.0±11.9; positive symptoms =13.3±3; negative symptoms =15.5±6. All patients were receiving fixed doses of an atypical antipsychotic. Groups were matched for mean age (t=−0.18, df=24, p=0.91; patients=32.2±8 yrs; controls=31.7±8 yrs). All subjects consented formally to participation.

2.2. Measures

Our primary behavioral measures of interest included total symptom scores on the Beck Depression (BDI-II) and Beck Anxiety (BAI) Inventories (data missing for 1 control), as well as the ‘total’ score; ‘self’ and ‘others’ subscales of the Level of Emotional Awareness Scale (LEAS; Lane et al., 1990; data missing for 4 controls). The LEAS is a 20-item observer-rated questionnaire that measures subjects’ emotional awareness using hypothetical (story) scenes to evoke four emotional judgments (anger, fear, happiness and sadness) at five-levels of increasing complexity. Ratings are made as first-person (How would you feel?) and third person accounts (How would the other person feel?). Score range from 1–100, with higher scores indicating greater emotional awareness.

2.3. Functional MRI

Our analysis of functional deactivations was based on an fMRI block-design study of the Multi-Source Interference Task (MSIT) (Bush and Shin, 2006). Briefly, during the MSIT, subjects responded to the identity (not the position) of a target number in a three-digit sequence corresponding to learned button box associations using the index (1), middle (2) and ring (3) fingers. During congruent trials, the target number always matched its appropriate button box position and was flanked by zeros (e.g. 0 2 0). During incongruent trials, the target never matched its appropriate position and was flanked by incongruent numbers (e.g. 3 1 1). Stimulus and inter-stimulus intervals were 2000 ms and 500 ms, respectively. While the primary application of the MSIT as an fMRI activation paradigm is to engage the dorsal AC cortex and a broader cognitive/attention-to-action network, it is also well suited for characterizing TIDs of ‘affective circuitry’ likely to involve the mPFC/rAC and PC/PrC regions (see Bush and Shin, 2006).

Task performance did not differ significantly between the groups in mean reaction-time (RT) interference scores (patients 363±57 ms; controls 350±91 ms; F=0.16, df=24, p=0.69) or total % errors (patients 5±8%; controls 3±3%; F=0.88, df=24, p=0.36). Two patients’ behavioral data were lost through technical difficulties. Functional MRI was acquired with a 3-Tesla GE Signa Horizon LX as a series of single shot gradient-recalled echo-planar imaging volumes (TR=3000 ms, TE=40 ms, flip-angle=60°; FOV =24 cm, voxel size =1.875×1.875×4.0 mm, 25 slices). Of the 220 volumes acquired, 160 represent the ‘activation’ component of the MSIT that incorporates 30-second blocks (i.e. 10 volumes) of alternating low-difficulty (‘baseline’) and high-difficulty (‘task’) trials (see Bush and Shin, 2006). These trials were preceded, split and ended with 20 volumes of visual resting-state fixation (‘rest’). Midline TID was examined by analyzing ‘rest’ and ‘task’ trials only (see also Kennedy et al., 2006).

2.4. Analysis

Spatial pre-processing and image analysis was carried out with SPM5 procedures (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/), involving motion correction, spatial normalization into a standard stereotactic space (MNI template) and smoothing using a 5 mm Gaussian kernel. Voxel-wise statistical parametric maps (SPMs) were then generated for each subject using the contrast ‘rest’–‘task’ trials. Resulting t maps were then entered into a 2nd level (whole-brain) random-effects group analysis (two-sample t-test; z score thresholds >2.5, p values >0.005, cluster- extents >8 contiguous voxels).

To extend the 2nd level analyses, we also performed region-of-interest (ROI) analyses of deactivations (% BOLD change, ‘rest’–‘task’) within the mPFC/rAC and PC/PrC regions using MarsBar software (http://marsbar.sourceforge.net). To ensure that the placement of ROIs sampled common variances to the patient and control...
groups, a conjunction analysis using SPMs of the minimum \( T \)-statistic over the patient and control deactivation contrasts was estimated. This enabled us to map peak co-ordinates of mPFC/rAC and PC/PrC deactivations that were highly and jointly significant to both study groups (for more detail, see Friston et al., 2005). Based on the conjunction analysis, subsequent \% BOLD signal changes were extracted from two spherical ROIs (10 mm) placed at the co-ordinates; \( x=0, y=45, z=5 \) (mPFC/rAC) and \( x=0, y=-50, z=36 \) (PC/PrC). Subjects’ fitted signal change values are expressed as a percentage of each scaled, mean ROI signal.

Finally, ROI \% BOLD signal change values were entered as dependent variables in stepwise linear regression models. Our predictor variables of interest included the behavioral measures introduced above, as well as task-performance (RT-interference scores) and, for patients’, positive and negative symptoms (PANSS) scores.

3. Results

3.1. Behavioral

Patients were not differentiated from controls in symptoms of depression (BDI-II; \( F=1.46, df=24; p=0.24 \); patients \( 8.3\pm8 \); controls \( 4.9\pm5 \)), anxiety (BAI; \( F=2.16, df=24, p=0.15 \); patients \( 7.4\pm6 \); controls \( 4.2\pm4 \)). Patients’ had lower mean scores all three measures of the LEAS, particularly LEA for ‘self’ (i) LEA for ‘self’, \( F=5.34, df=22, p=0.03 \); patients \( 49.2\pm9 \); controls \( 57.9\pm6.3 \); (ii) LEA for ‘others’, \( F=1.67, df=22, p=0.21 \); patients \( 46.3\pm10 \); controls \( 52.1\pm10 \); (iii) LEA ‘total’, \( F=3.93, df=22, p=0.06 \); patients \( 56.8\pm8 \); controls \( 63.3\pm7 \)).

3.2. Functional MRI

Functionally, both groups showed the characteristic pattern of midline TID, predominately in rAC to mPFC

Fig. 1. Task-induced deactivation of midline cortical regions in schizophrenia patients and controls subjects and behavioral correlates in patients. Functional results are displayed on sagittal sections of a structural MRI of a single-subject given in standard space (Colin27, Montreal Neurological Institute). Functional results given as ‘Sz-Patients’ and ‘Controls’ correspond to within-group results (displayed at \( z \) scores \( >2.3 \) to \( 5 \)). For patients, anatomical co-ordinates for peak deactivations of our major areas of interest were; rAC/mPFC, \( x=-4, y=40, z=12 \), \( z \) score=3.35, \( p<0.0001 \) and PrC/PC, \( x=-6, y=-46, z=44 \), \( z \) score=3.93, \( p<0.0001 \). For controls, these corresponded to; rAC/mPFC, \( x=0, y=48, z=4 \), \( z \) score=2.5, \( p<0.005 \) and PrC/PC, \( x=0, y=-50, z=36 \), \( z \) score=2.67, \( p<0.004 \). The functional overlay given as ‘Sz-Patients’>‘Controls’ corresponds to a between-group difference, reflecting greater TID of anterior and posterior midline regions in schizophrenia patients, including the PC and rAC/mPFC subregions (displayed at \( z \) scores \( >2.3 \) to \( 4 \)). These differences corresponded to peak deactivations at; rAC/mPFC, \( x=-2, y=38, z=20 \), \( z \) score=2.78, \( p<0.003 \) and PC, \( x=-6, y=-44, z=34 \), \( z \) score=3.39, \( p<0.0001 \). Accompanying scatter-plots display significant correlations of \% signal change deactivation of rAC/mPFC ROI with patients’ scores on LEA for ‘others’ subscale and reaction-time (RT) interference scores.
as well as PrC to PC (results summary in Fig. 1 caption). Between-group comparison indicated significantly greater TID of both regions in the patient group.

3.3. Brain-behavioral associations

For control subjects, task-performance (RT-interference) showed a significant predictive association for the PrC/PC ($F(1,9)=5.75$, $p<0.043$) explaining $34.6\%$ (adjusted $R^2$ statistic) of the modeled variance with a zero-order correlation coefficient of $r=-0.65$. There was no significant predictor of the magnitude of % BOLD deactivation in the rAC/mPFC.

For patients, task-performance (RT-interference) and LEA for ‘others’ showed a significant predictive association with the magnitude of % BOLD deactivation in the rAC/mPFC region ($F(1,9)=10.79$, $p<0.007$) explaining $68.5\%$ of the modeled variance (adjusted $R^2$ statistic) with zero-order correlation coefficients of $r=-0.65$ (RT-interference) and $r=0.69$ (LEA for others). There was no significant predictor of the magnitude of % BOLD deactivation in the PrC/PC region.

4. Discussion

In this preliminary study, we examined the nature of task-induced deactivations (TIDs) of midline cortical regions in schizophrenia patients with fMRI. Our primary finding was that patients showed a more pronounced pattern of midline TID compared to control subjects, involving the rostral anterior cingulate (rAC)/medial prefrontal cortex (mPFC) and precuneus (PrC)/posterior cingulate cortex (PC). For patients, the magnitude of TID in the rAC/mPFC region was explained, in part, by their relative level of task performance as well as scores on the LEA for ‘others’ subscale.

The mechanism proposed to explain midline TIDs relates to the change of brain activity that occurs when one’s attention is shifted from the normally self-focused state of attention at rest or low cognitive demand conditions, to externally-focused attention when performing cognitively demand task (Raichle et al., 2001; Gusnard et al., 2001a,b). The greater cognitive load of the task, the greater interruption of self-directed attention, and larger TID effect observed (McKiernan et al., 2003). Interestingly, in situations where one’s shift of attention is less effective between rest and cognitive task conditions, or lapses during task, less TID of midline regions has been reported (i.e., slower RT scores predict less TID; Lawrence et al., 2003; Weissman et al., 2006). For patients, this relationship was observed in the rAC/mPFC region, where the magnitude of TID was negatively correlated with task RT scores. For controls, this pattern also existed but for the PrC/PC region only, consistent with a recent fMRI study in healthy subjects (Weissman et al., 2006). Thus, overall, these results suggest a dual-influence of task on TID of the rAC/mPFC in schizophrenia patients, where the greater relative TID of this region presumably reflects a greater general experience of task demand compared to healthy subjects. In this context, moreover, patients showing relatively poorer task performance showed a less pronounced TID effect — a pattern that has been linked to more frequent attentional lapses or intrusion of self-directed thought during cognitive performance (Weissman et al., 2006).

In addition to task performance, we also observed that patients’ magnitude of deactivation of the rAC/mPFC was associated with their scores on the LEAS (Lane et al., 1990), specifically their level of emotional awareness for others. This finding is interesting to consider with reference to neuroimaging studies of alexithymia, where structural and functional alterations of the rAC and mPFC regions have been linked to the characteristic inability of alexithymic subjects to identify and verbalize emotional states of self and others (Berthoz et al., 2002; Gundel et al., 2004; Kano et al., 2003; Lane et al., 2000; Moriguchi et al., 2006). Decreased emotional awareness for others has been illustrated, for example, in Theory of Mind (ToM) tasks, where the poor performance of alexithymic subjects has been associated with reduced activation of the mPFC (Moriguchi et al., 2006). Because alexithymia appears to co-occur at high levels schizophrenia patients (Cedro et al., 2001), who also show well-known deficits on ToM tasks (Brune, 2005), there may be some relevance of these dimensions to the current findings. Further studies will be needed to clarify how these and other aspects of the emotional disturbance seen in schizophrenia may be expressed in these prefrontal TIDs and whether a reduced capacity for TID predicts poorer functioning patients in these domains, as suggested by our data.

Overall, these results suggest a complex interchange between cognitive and emotional influences on midline cortical deactivations in schizophrenia, which in this study, were not modulated by patients’ symptom severity. Typical task-oriented fMRI studies may benefit from a more detailed consideration of this TID phenomenon and how it relates to the level of emotional disturbance of the patient. Such studies should also be extended to include female patients as well as examining the influence of patients’ medication status.
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