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Schizophrenia and frontal cortex: Where does it fail?

P. Salgado-Pineda [a], A. Caclin [b,c,d], I. Baeza [e], C. Junqué [e], M. Bernardo [e], O. Blin [a], P. Fonlupt [b,c,d,*]

[a] *Institut des Neurosciences Cognitives de la Méditerranée, Faculté de Médecine, Université de la Méditerranée, UMR 6193 CNRS, Marseille, F-13385, France*
[b] *INSERM, U821, Lyon, F-69500, France*
[c] *Institut Fédératif des Neurosciences, Lyon, F-69000, France*
[d] *Université Lyon 1, Lyon, F-69000, France*
[e] *Department of Psychiatry and Clínical Psychobiology, University of Barcelona, Institut d'investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, S-08036, Spain*

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Abstract

Schizophrenia is characterized by cognitive, social, and emotional impairments and by psychotic symptoms. Neuroimaging studies have reported abnormalities within the prefrontal cortex and it has been hypothesized that schizophrenia results from poor or miswired anatomical/functional connections. We have compared the functional connectivity within the frontal cortex in control and schizophrenic subjects during the realization of a Continuous Performance Task. The connectivity pattern within the frontal cortex was uncovered by the analysis of the correlation matrix computed from the fMRI time series in frontal areas for 14 schizophrenic patients and 14 control subjects. In control subjects, the right dorsolateral prefrontal cortex (DLFCr) activity correlated i) positively with the left dorsolateral prefrontal cortex and the posterior part of the supplementary motor area, ii) negatively with the medial and anterior/inferior part of the frontal cortex. In the schizophrenic group, these relations were abolished or strongly lowered. The negative relation between the DLFCr and the medial frontal cortex has been proposed to play a key role in setting a harmonious balance between the direction of attention to the external world and the expression of the individual believes and self-referential activities, and therefore, the impaired relation of right DLFCr with other frontal areas could explain a distorted perception of external world in relation with internal motivations.

Keywords: Schizophrenia; Attention; Continuous performance task; Prefrontal cortex; Functional magnetic resonance imaging; Functional connectivity

1. Introduction

Schizophrenia is a psychiatric disorder characterized by cognitive, social, and emotional impairments and by psychotic symptoms (Carpenter and Buchanan, 1994). The availability of imaging techniques has allowed to search for neural correlates of such a disorder and in the last 20 years an increasing number of reports have described anatomical and functional differences in brain organization between schizophrenic patients and control subjects. Moreover, the large variety of symptoms associated with this pathology has given rise to the hypothesis that schizophrenia results more from poor or miswired

* Corresponding author. INSERM U821, Centre Hospitalier le Vinatier, Bâtiment 452, 95 Boulevard Pinel, 69675 BRON CEDEX, France. Tel.: +33 6 60 54 68 29; fax: +33 4 72 13 89 01.
E-mail address: fonlupt@lyon.inserm.fr (P. Fonlupt).

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anatomical/functional connections than from particular and localized defects (Foucher et al., 2005). Among the numerous characteristics of the illness, a constant feature is a difficulty in prioritizing, processing, and responding to information (Andreasen, 1993; Kapur, 2003). As the prefrontal cortex is a key structure in such cognitive abilities (Miller et al., 2002; Rushworth et al., 2004) it is not surprising that abnormalities have been described within this area in schizophrenic patients.

Connectivity studies (using fMRI) in schizophrenic patients have mostly been devoted to the analysis of the relations between frontal areas and other brain areas, and have revealed abnormal connections between frontal areas and both cortical and subcortical structures (Foucher et al., 2005; Honey et al., 2005; Whalley et al., 2005). Such impaired relations are likely to underlie some of the deficits observed in this pathology, in particular attentional deficits. Nevertheless, it is also worth noting that a number of studies have reported a dysfunction within the frontal lobes, revealing modified levels of activity in frontal regions in schizophrenic patients compared to control subjects in a variety of tasks (e.g., Holmes et al., 2005; Perlstein et al., 2003). This suggests the existence of selective defects within frontal regions in schizophrenia. We further know that in normal subjects, there exist relations between frontal areas, and these relations are involved in attentional control. In particular, the dorsolateral prefrontal cortex is more activated when attention is focused on sensory events whereas the medial prefrontal cortex is more activated during self-referential tasks (Gusnard and Raichle, 2001; Wicker et al., 2003), and importantly the activities of these areas are negatively correlated (Caclin and Fonlupt, 2006a; Chaminade and Fonlupt, 2003). We therefore undertook a study of the relations between frontal areas in schizophrenia, in order to assess whether this pattern of functional connectivity within frontal lobes is altered in the disease. Anatomical evidence for a deficit of connectivity within the frontal areas can be found in a study by Paillère-Martinot et al. (2001), in which using voxel-based morphometry, a selective reduction of regional white matter volumes was found in the frontal lobes in a group of schizophrenic patients when compared to healthy control subjects.

In the present study, our aim was to establish the functional connectivity pattern in frontal areas during realization of a CPT (Continuous Performance Task) in healthy subjects, and to determine whether the same pattern can be observed in schizophrenic patients. The CPT was chosen because this task typically requires to assign salience to an external object in relation with an internal goal (to decide if the current object is identical to the precedent) and has been extensively studied in schizophrenia using functional neuroimaging since 1990 (Buchsbaum et al., 1990). Functional neuroimaging studies during CPT in schizophrenia research have been carried out using single photon emission tomography (SPECT) (Berman and Weinberger, 1990), positron tomography (PET) (Buchsbaum et al., 1990, 1992; Cohen et al., 1997; Katz et al., 1996; Siegel et al., 1993; Schröeder et al., 1994), and fMRI (Salgado-Pineda et al., 2004; Volz et al., 1999). One of the most consistent results of these investigations has been a decreased activation for the schizophrenic patients during test performance in the frontal cortex. Frontal hypometabolism was similar in medicated and never-medicated patients (Buchsbaum et al., 1990, 1992). Thus, due to both the implied cognitive processes and the repeatedly reported modification of the evoked hemodynamic response in the frontal cortex in schizophrenic patients, CPT is a good candidate for studying a potential modification of connectivity within the frontal cortex in schizophrenia. CPT may be the most popular clinical measure of sustained attention (vigilance). The basic CPT paradigm involves selective attention in response to an infrequently occurring stimulus (for a review, see Riccio et al., 2002). More precisely, the interest of the CPT is that it requires the subject to focus his/her attention towards external events, and it has been shown that, in normal subjects, directing one's attention towards the sensory scene relies on a balance between frontal areas (as discussed above, see Caclin and Fonlupt, 2006a; Chaminade and Fonlupt, 2003).

To study the connectivity within the frontal cortex during the realization of a CPT, we have reanalyzed the data of a previously reported study including 14 controls subjects and 14 schizophrenic subjects performing a simplified CPT (Salgado-Pineda et al., 2004). The strategy used in the analysis was i) to focus on the frontal cortex (by masking other regions of the brain), ii) to isolate VOIs (Volumes of Interest) on the basis of control subjects data, with the constraint that the variations of activity with the task of the voxels constituting each VOI should be homogeneous (i.e. voxels have similar variations of activity between the CPT and the control task), iii) to determine the correlation pattern between these VOIs in the control subjects, and iv) to compare this pattern for the control subjects to the pattern for the schizophrenic patients.

2. Methods

In this study which aimed at comparing the connectivity pattern in the frontal areas between control subjects and schizophrenic patients, the most crucial methodological choices concern the selection of the