Schizophrenia and frontal cortex: Where does it fail?

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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.

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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
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; Schröder 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
VOIs entered in the connectivity analyses and the statistical method used to uncover the connectivity. VOIs selection can be done according to functional and/or anatomical criteria, and in the case of a functional criterion, can be based either on the data from only one or both groups of subjects. We chose to delineate VOIs according to a functional criterion in the control subjects data. Using a functional criterion, namely the difference between the CPT and the control task, allows to focus on the frontal areas engaged in the CPT. The reason for delineating VOIs based on the control subjects data is that it allows to test a neatly circumscribed question: is the connectivity pattern for schizophrenic patients similar to that of control subjects? Defining VOIs separately for the two groups would preclude any direct statistical comparison between the two groups, and finally, selecting VOIs according to both control and patients data leads to an uncomfortable situation where the connectivity pattern studied involves areas selected on the basis of both normal and pathological brain functioning. Our approach therefore does not aim at uncovering the connectivity pattern between frontal areas engaged in the CPT in schizophrenic patients but rather aim at specifying if relations between frontal areas observed in control subjects are modified in schizophrenic patients.

Connectivity in fMRI experiments can be studied in two ways: either using data-led methods such as principle component analysis (PCA) to summarize “functional” connectivity or by specifying an anatomical (constraining) model and testing it, using for example structural equation modelling, to uncover the “effective” connectivity. Effective connectivity analyses requires in particular to formulate hypothesis regarding which areas are connected and the direction of these connections. Studies of the effective connectivity within the frontal lobe are fairly rare, and constructing an anatomical model of the connections between the frontal areas studied here would be difficult, which makes the study of functional connectivity a more natural choice. The present study uses a functional connectivity approach and thus does not make any a priori assumption about the direction of the connections. PCA is the most widely used method to study functional connectivity, and allows to decompose neuroimaging data into a set of modes (Worsley et al., 1997). A limit of this approach is that interpreting the results is difficult when one has to take into account many of the components resulting from the PCA to explain a large part of the variance in the data. We therefore used a more flexible method relying on a spectral reordering of the correlation matrix (the correlation coefficients between the time courses of activities of the different frontal VOIs studied), as described in Johansen-Berg et al. (2004).

2.1. Participants

Fourteen right-handed patients, seven men and seven women, mean (±SD) age 25 (±4) years with a DSM-IV diagnosis of schizophrenia were included in the study. They were recruited in the Psychiatry Service of the Hospital Clinic of Barcelona. They were all receiving neuroleptic medication at the time of examination and the diagnoses were confirmed by two psychiatrists at the study entry and one year later. There were no co-morbid psychiatric diseases for any patient. All except three of the schizophrenic patients were diagnosed as paranoid (one was residual and two undifferentiated). A full description of the clinical characteristics of the 14 patients can be found in Salgado-Pineda et al. (2004). 14 healthy control subjects were matched to the patients for handedness, age, sex and parents’ socioeconomic status (expressed as the highest level of education completed by either parent). The study was approved by the ethics committee at the Barcelona Hospital and all subjects gave informed consent to participate in the study.

2.2. fMRI protocol

The experiment was composed of two blocks of a control task alternated with two blocks of the CPT. A control block consisted of the same stimulus (the number “1”) repeated 40 times: the digit appeared on the screen for 2500 ms followed by a dark screen time of 500 ms. Subjects were asked to respond every time that the number one appeared. The duration of the block was 120 s. A CPT block consisted of a 220 s presentation of a series of one digit numbers. Each stimulus appeared on the screen for 100 ms followed by a dark screen for 1000 ms. Subjects were asked to respond when the same digit appeared twice in succession. Target probability was 20% (40 targets out of 200 stimuli). Note that with this design, as the subjects should push the response-button more often in the control task than in the CPT (one response every 1100 ms vs. one response every 5500 ms on average), a higher activity in motor areas during the control task than during the CPT was expected. This procedure allows to confirm a posteriori the efficiency of the analyses strategy, as this difference in activity between the tasks in motor areas should be recovered.

All data acquisition was performed on a GE Signa 1.5T clinical scanner (General Electric, Milwaukee, WI). fMRI scans were acquired using a T2*-weighted EPI sequence (TR = 2000 ms; TE = 40 ms; FOV = 24 × 24 cm;
64 × 64 matrix; flip angle=90°). Images were composed of 20 axial slices with a slice thickness of 5 mm and an interslice gap of 1.5 mm.

2.3. fMRI data analysis

The first level of data processing has been extensively described in a previous report (Salgado-Pineda et al., 2004). Briefly, the data were pre-processed (intra-subject realignment, normalization in MNI space, and smoothing) with SPM2 software (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab® and the functional data were analyzed using a general linear model (GLM, see Friston et al., 1995; Wicker and Fonlupt, 2003). As our aim was to study the brain activity linked to the sustained attention during CPT task (compared to the control task), the first 16 scans of each of the four blocks were discarded in order to eliminate the periods of transition between the two tasks. Thus, a control block was composed of 44 scans, a CPT block of 94 scans, and the full experiment of 276 scans (2 blocks of each task). The time series were analyzed using a GLM. The confound part of the design matrix modeled the average value of each scan and the two repetitions of the two tasks (i.e. the two halves of the experiment). This removed the global signal variation and the variations that were not linked to the nature of the task. The part of interest of the design matrix modeled the nature of the task with four columns (one for each block) and thus we took into account the variations due to the task performed, and also allowed the variations between the two tasks to be different during the two halves of the experiment. We used a mixed-effect model allowing for inference about the population by taking into account inter-subject variance (called “random-effect analysis” in SPM software) when calculating the t-values corresponding to the difference of activity between the control condition and the CPT condition.

2.4. Selection of volumes of interest and preparation of the correlation matrix

As our aim was to study exclusively the connectivity within the frontal cortex, we first applied a mask created using MAasks for Region of INterest Analysis software (MARINA: http://www.bion.de/Marina.htm). The mask included bilaterally the Inferior Frontal Gyrus, Medial Frontal Gyrus, Middle Frontal Gyrus, Superior Frontal Gyrus, and Precentral Gyrus (53331 voxels).

As mentioned earlier, VOI selection followed a functional criterion to associate voxels, namely the difference between the CPT and the control task in the control group. We constructed VOIs based on the confidence that there was a difference between the two tasks at each voxel (i.e. based on the t-value in the CPT minus control task contrast). Compared with a procedure relying directly on the average signal difference (not divided by the residual variance) between the two tasks at each voxel, it limits the importance of the voxels where the signal is the noisiest. Finally, to delineate VOIs one has to specify a limit to stop associating voxels. This limit was here the size of the resulting VOIs, which was constrained to be homogeneous to avoid signal-to-noise ratio variations across VOIs.

In practice, we thresholded the t-map in decreasing steps (until t = 1.96) to uncover successively VOIs with similar sizes (from 80 to 160 voxels) and with homogeneous t values for all the voxels included in the VOI. With this procedure, 55 VOIs were recovered and the time series of each VOI was represented by the average of the time series of its constituting voxels.

The time series have to be preprocessed prior to the connectivity analysis itself, to remove confounding variations. Global variations (in particular due to scanner gain fluctuations) were removed by scaling. In this experiment, several factors are likely to explain signal variations: task effects, block effects (i.e. differences between the two halves of the experiment), and Task × Block interaction (i.e. the variations between the two tasks can be different in the two halves of the experiment). Each VOI time series was subjected to a GLM with Block (modeling the two halves of the experiment) as a confounding factor and Task and Task × Block as factors of interest. The correlation matrix was computed for the time series corresponding to the resulting fitted values (i.e. variations in the time series that are explained by the GLM). Fitted values thus took into account task effects and task-by-block effects, but not block effects (see Caclin and Fonlupt, 2006b, for a more detailed discussion regarding time series preparation prior to connectivity analyses).

2.5. Analysis of the correlation matrix

The correlation matrix (55 rows, 55 columns) was reordered using a spectral reordering algorithm. This method was originally designed to reduce the envelope of sparse matrices (Barnard et al., 1995). It has recently been applied to neuroimaging data to separate groups of VOIs (Johansen-Berg et al., 2004). This method finds the reordering (i.e. a permutation of the rows and the column) that minimizes the sum of element values multiplied by the squared distance of that element from...
the diagonal. Simply speaking, the method forces large values toward the diagonal, and if the data contains group of VOIs, these groups will appear in the reordered matrix (Johansen-Berg et al., 2004).

3. Results

In control subjects, the contrast “CPT minus control task” allows to select voxels belonging to the frontal areas which exhibit an increase or a decrease in activity during the CPT compared to the control task. The regions showing increased activity during CPT are comparable to those previously described (Salgado-Pineda et al., 2004). As described in the Methods section, 55 VOIs with a difference in activity between the two tasks were isolated in the frontal areas and the resemblance of their time series was assessed according to the method described by Johansen-Berg et al. (2004).

Firstly, we verified that with the data of the control subjects group a coherent pattern of connectivity within

![Fig. 1. Connectivity-based separation of 55 frontal VOIs. The time series for each VOI was composed by the concatenated time series (fitted values of the GLM) of 14 control subjects (panel A) or of the concatenated time series of 14 schizophrenic subjects (panel B). The reordered connectivity correlation matrix is shown under the label (A or B), with positive (negative) correlation coefficients in red (blue). The groups of VOIs identified in the reordered matrix are indicated by the colored bar below the matrix and are represented on the template from the MNI. The VOIs appearing in bright colors constitute the core of the group whereas those in dark colors are those which are poorly classified.]
the frontal areas is uncovered using this method. The reordering of the correlation matrix composed of the correlation coefficients between the time series (fitted values resulting from the GLM) in the 55 frontal VOIs allowed to separate these VOIs in two groups (Fig. 1A).
The first group (green) comprises dorsolateral prefrontal, inferior frontal, and anterior preSMA areas, and the second group (red) included anterior/medial frontal areas, premotor areas, and inferior/posterior part of inferior frontal regions.

The six clusters were located as follows: DLFCr: right Dorsolateral prefrontal cortex (stereotaxic coordinates (mm) in the MNI reference brain provided with SPM2: 48 8 36); DLFC1: left Dorsolateral prefrontal cortex (−45 2 35); pSMA: Superior frontal gyrus (5 11 58); MeF: Medial frontal gyrus (−9 56 27); IFGa: right Inferior frontal gyrus, anterior (43 26 7); IFGp: right Inferior frontal gyrus, posterior (49 −3 11). The correlation coefficients were computed from the time series formed by the fitted values (resulting from the GLM) for each of the subjects (14 values for the control group and 14 values for the schizophrenic group). The first value is the mean correlation coefficient for the control group and the second value is the mean correlation coefficient for the schizophrenic group. Significant differences between groups (Mann–Whitney U test, \( p < 0.05 \)) are indicated with an asterisk.

4. Discussion

Based on the modifications of cerebral activity during a continuous performance task realized by control subjects, we have isolated 55 VOIs in the frontal cortex with similar sizes and with homogeneous \( t \) values within each VOI. In control subjects, the rearrangement of the correlation matrix of the time series of these VOIs allows to separate two groups of VOIs (Fig. 1A). The first group (in green) included the areas implicated in goal-directed attention processes: anterior pSMA, dorsolateral prefrontal cortex, and inferior frontal cortex. The second group (red) included areas implicated in self-directed attention located in the medial and anterior parts of the frontal lobe, areas implicated in movement processes: posterior pSMA and premotor cortex, and the posterior part of the inferior frontal gyrus. This result is congruent with an organization of the human brain in anticorrelated functional networks (Fox et al., 2005): on the one hand, areas implicated in goal-directed attention exhibit increased activity during the CPT and on the other hand, areas implicated in the monitoring of internal goals showed a decreased activity during the CPT. These last areas included the medial/anterior frontal areas, that have been repeatedly showed as exhibiting decreasing activity during active tasks versus resting state (Gusnard and Raichle, 2001; Wicker et al., 2003). The presence of the motor-
related areas, posterior pSMA and premotor cortex (which are less active during the CPT) within this group of VOIs can be explained by the paradigm used, which required less responses from the subject during the CPT (40 during 220 s) than during the control task (80 during 120 s), and hence there were different demands on the motor system during the two tasks. This comforts the efficiency of the analysis method because it allows to capture this feature of the paradigm.

Applying the same procedure to the data of the schizophrenic patients conducted to a sensibly different result. The separation of the VOIs in two sub-groups was far less clear and we were unable to allocate a lot of VOIs to one of the two groups, in particular the VOIs of the right dorsolateral frontal areas and the inferior/ anterior frontal areas (Fig. 1B).

To investigate more deeply these differences, we have merged the 55 initial VOIs into 6 larger clusters (MeF, DLFCr, DLFCl, pSMA, IFGa, IFGp) according to their belonging to the groups of clusters found when reordering the correlation matrix and to their spatial proximity in the brain. We have extracted for each cluster the time series relative to the variations of activity related to the tasks (fitted values) and compared the correlation matrix obtained for the control and schizophrenic groups. In the control group, we found a strong mutual positive influence between the DLFCr, DLFCl, IFGa and anterior pSMA. The DLFCr has been repeatedly shown to be activated by sustained attention to the visual modality (Mazoyer et al., 2002; Rees et al., 1997; Rees and Lavie, 2001), memory retrieval (Gallo et al., 2006; Nyberg et al., 1996), and more generally form part of the anterior system that plays a role in the voluntary control of focused attention (Posner and Petersen, 1990). The DLFCl can be associated to the general attention required by the CPT as well as to a more specific requirement of verbal material processing due to the presentation of digits. The anterior pSMA has been associated with decision making during a conceptual task, as opposed to motor control (Johansen-Berg et al., 2004). The IFGa has been associated with allocating attention in various tasks (Binder et al., 2004; Lipschutz et al., 2002). Activities of the MeF and IFGp were positively correlated with each other during CPT and negatively correlated with the four other areas. MeF activity has been reported to increase during the attention shift from external (environment) to internal (self) goals and to exhibit variations opposite to that of dorsolateral-, inferior-prefrontal areas and the anterior part of the SMA (Fox et al., 2005; Gusnard and Raichle, 2001; Mechelli et al., 2005; Wicker et al., 2003). It is more difficult to find reports concerning the IFGp. The area we pointed out is located at the crossroad of the inferior frontal gyrus, the insula, and the temporal gyrus, and may have been labeled differently in the literature. Interestingly, a negative correlation of dopamine binding and novelty seeking rating has been observed in this region for control subjects (Kaasinen et al., 2004).

More generally, the six clusters investigated exhibit in the control group a correlation pattern which is in full agreement with the general organization of the frontal cortex in two separate modes proposed previously (Fox et al., 2005; Gusnard and Raichle, 2001; Wicker et al., 2003). More precisely, we show again the separation of the networks involved in internal versus external goal-directed tasks (Gusnard and Raichle, 2001; Wicker et al., 2003) or self versus others (environment) distinction (Ruby and Decety, 2004; Schmitz and Johnson, 2006; Wicker et al., 2003).

In schizophrenic patients the pattern of correlations within these six clusters in frontal regions was different from that of control subjects. The main difference is the severe weakening of the correlations between DLFCr and other areas during the CPT (see Table 1): both the positive relation with DLFCl and pSMA and the negative relations with MeF and IFGp are almost absent. Moreover, the positive relation between IFGp and MeF decreased in comparison to the control group, and the negative relation between IFGp and IFGa became positive.

As always in connectivity studies, the intermediate involvement of other brain structures in the altered connectivity pattern observed here within frontal regions cannot be excluded. Nevertheless, the hypothesis of direct links between frontal areas is not a unrealistic one, given the involvement of these regions in complex cognitive abilities. Further in healthy subjects, connections between frontal areas (such as the negative relation between DLFC and MeF) have not been found to be mediated by other brain structures in connectivity studies which have considered larger sets of brain regions.

Observing differences between a group of control subjects and a group of schizophrenic patients always rise the question of whether these differences are a genuine consequence of the disease or an effect of the administered drugs. However, although the results are not directly comparable to the present results, we may note that frontal hypometabolism measured by PET during realization of a CPT appears similar in medicated and never-medicated patients (Buchsbaum et al., 1990, 1992). Moreover, the effects of drug treatment would be expected large and
poorly located in contrast with the observed focal modifications of connectivity. Another issue is whether the effects observed in such a study are specifically linked to the positive or negative symptoms. The patients exhibited indeed both types of symptoms. In a follow-up analysis not reported in detail here, we did not find any significant correlations between the strength of the relations between frontal areas and clinical scores (SANS and SAPS). Nevertheless with only 14 patients, a subtle link between positive or negative symptoms and the observed altered patterns of connectivity would not be detectable. For a disease as complex as schizophrenia it is always difficult to generalize a result obtained with a particular sample of patients, yet the anomalies in the relationships between frontal structures that we observed might underlie a key deficit of this pathology. These anomalies are indeed related to the process of sustained attention measured by the CPT test, which is recognized as generally impaired in this pathology.

The modifications of the connectivity within the frontal lobe appear as a good support of some cognitive dysfunctions observed in schizophrenia. The efficient behavior needed to realize a task implying attention mobilization has been proposed to rely on a harmonious balance between the activities of the different parts of the frontal cortex. The role of the right dorso-lateral prefrontal cortex in the direction of attention to the external world is widely recognized, while the role of medial frontal structures in the expression of the individual believes and self-referential activities is strongly suggested. The impaired relation of right DLFC with other frontal areas could therefore be related to the false believes, delusions and, more generally, a distorted perception of external world in relation with internal motivations.

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