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Neural correlates of planning performance in patients with schizophrenia — Relationship with apathy

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ABSTRACT

Patients with schizophrenia often suffer from apathy: a quantitative reduction of voluntary, goal-directed behaviors that impairs daily functioning. We hypothesized that schizophrenia patients with high levels of apathy would show decreased activation in brain regions involved in planning and goal-directed behavior.

Patients with schizophrenia or psychotic spectrum disorder (n = 47) and healthy controls (n = 20) performed the Tower of London (ToL) task during fMRI scanning using arterial spin labeling. To investigate the relationship between apathy and planning in patients, a proxy measure of apathy based on the Positive and Negative syndrome Scale was regressed against the task-related brain activation. Brain activation was also compared between patients and healthy controls.

Higher levels of apathy were associated with less task-related activation within the inferior parietal lobule precuneus and thalamus. Compared to controls, patients showed lower activation in lateral prefrontal regions, parietal and motor areas, and a higher activation of medial frontal areas.

Apathy was related to abnormal activation in thalamus and parietal regions during the ToL task. This supports the hypothesis that impaired function of brain regions involved in planning and goal-directed behavior may underlie apathy in schizophrenia. Moreover, impaired lateral prefrontal activation in schizophrenia patients compared to controls is consistent with the hypofrontality model of schizophrenia. In contrast, stronger medial frontal activation in patients may be related to increased effort to perform a task with conflicting task solutions.

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1. Introduction

Patients with schizophrenia frequently experience markedly reduced levels of interest and a lack of initiative in daily activities, which is a hallmark of apathy. Apathy is a core feature of negative symptoms in schizophrenia (Foussias and Remington, 2010). Research has shown that 30% of the patients with a first episode psychosis show enduring levels of apathy (Faerden et al., 2010). Understanding apathy in schizophrenia has important implications, as it has been argued to be the critical component, especially with regard to poor (social) functioning, unemployment, severity of illness and poor functional outcome (Bottlender et al., 2010; Faerden et al., 2010; Foussias and Remington, 2010; Kiang et al., 2003).

Apathy can be described as a quantitative reduction of voluntary, goal-directed behaviors. Levy and Dubois (2006) state that apathy may arise from "planning and working memory impairments, through difficulties in sequencing ideas, maintaining mental representation of goals and sub-goals and manipulating them, may abort the elaboration of goal-directed behaviors, thereby quantitatively (and qualitatively) reducing goal-directed behaviors". In this view apathy may be rooted, in part, in planning deficits. Planning has been defined as "the goal-directed, trial-and-error exploration of a tree of alternative moves" (Dehaene and Changeux, 1997). Indeed, a direct relation between apathy and executive function or goal-directed behavior has also been observed (Faerden et al., 2010; Foussias and Remington, 2010; Roth et al., 2004), but the neural correlates of this association, to the best of our knowledge, have not been investigated as yet.

Goal-directed behavior and executive functioning are both regulated by a fronto-striatal-parietal brain circuit (Fuster, 2009; Goldberg, 2009) and a similar brain circuit has been implicated in apathy (Levy and

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Dubois, 2006). Impaired function of a fronto-striatal-parietal network may thus be related to apathy as a consequence of problems in goal-directed behavior (Konstantakopoulos et al., 2011; Roth et al., 2004). Schizophrenia patients with deficit syndrome, showing high levels of negative symptoms, including apathy, have shown abnormal regional cerebral blood flow (Lahti et al., 2001) and white matter deficits (Rowland et al., 2009) in fronto-parietal regions. Moreover, higher levels of apathy in schizophrenia have been related to decreased gray matter volumes in these areas and to neuropsychological deficits (Roth et al., 2004). In the current paper we address the question whether hampered activation of this fronto-striatal-parietal network during planning may be associated with apathy in schizophrenia.

The Tower of London task (ToL) is a suitable task to investigate higher order planning processes in fronto-striatal-parietal brain circuits as it requires subjects to perform a set of subsequent mental operations that involve planning (Shallice, 1982) and thus resembles the definitions of planning and apathy as defined above (Baker et al., 1996; Beauchamp et al., 2003; Unterrainer and Owen, 2006; Wagner et al., 2006). An early PET study using the ToL has shown decreased medial prefrontal activation in schizophrenia, related to the severity of negative symptoms (Andreasen et al., 1992). A more recent fMRI study reported some evidence for prefrontal dysfunction in schizophrenia, but these results were not unequivocal (Rasser et al., 2005).

The ToL has also been used to study frontal lobe lesions, which are characterized by apathy and impaired organizational abilities (Owen et al., 1996). Patients with frontal lobe damage show impaired performance on the ToL task (Dehaene and Changeux, 1997) similar to schizophrenia patients (Morris et al., 1995; Pantelis et al., 1997). Moreover, patients with depression (Elliott et al., 1997) and Parkinson's disease (Dagher et al., 2001; Owen et al., 1996) – both involving apathy and anhedonia – also showed frontal, parietal and striatal dysfunction during the ToL task. Taken together, these findings suggest that apathy in schizophrenia may be related to planning impairments associated with dysfunction of frontal, parietal and striatal connections.

We hypothesized that schizophrenia patients with high levels of apathy would show impaired function of fronto-striatal-parietal brain areas involved in planning. We included a task with different levels of difficulty (1–5 move problems) (Dagher et al., 1999; Schall et al., 2003) to account for differences in task performance between study participants. Furthermore, a healthy control group was included for reference.

2. Methods

2.1. Subjects

Baseline fMRI data of two trials were combined, i.e. before any intervention took place. The first trial that investigated the effects of treatment with aripiprazole compared to risperidone on negative symptoms (EUDRA-CT: 2007-002748-79). The second fMRI study was part of a double-blind multicenter randomized controlled trial investigating the effect of rTMS on negative symptoms (Dutch Trial Registry: NTR1261). The procedures for the baseline measurements used in the current study were identical for both studies. The studies were executed in accordance to the declaration of Helsinki and approved by the local ethical committee of the University Medical Center of Groningen. Patients in these trials (n = 47) were recruited from mental health care centers in the northern part of the Netherlands. Participating subjects gave oral and written consent after the procedure had been fully explained. Diagnosis was confirmed with the Schedules for Clinical Assessment (SCAN 2.1) diagnostic interview (Giel and Nienhuis, 1996). All patients met DSM-IV criteria for a diagnosis of schizophrenia or a related non-affective psychotic disorder. A comorbid depression or history substance abuse (>6 months before) was allowed. Patients had to abstain from drugs and alcohol 24 h before testing. Severity of symptoms was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

Healthy controls (n = 20) did not differ from to the patients in age, gender, education level and handedness. Since part of the subjects was young and had not finished education, the highest education level that a subject finished or expected to finish was recorded according to Verhage (range: 1. elementary school to 8. university) (Verhage, 1984). Age and education level were compared between patients and controls with a Mann–Whitney *U* test and gender and handedness with a Chi-square test for independence.

Exclusion criteria for both patients and healthy controls included age <18 or >60, MRI incompatible objects (e.g. medical pumps, prostheses, piercings, red tattoos), (suspected) pregnancy, claustrophobia, history of neurological abnormalities (e.g. epilepsy), history of severe head injury, brain infarction, and inability to provide informed consent.

2.2. Task design

The task analyzed in this paper was the first scan in an MRI protocol that subsequently included an anatomy scan, a socio-emotional task, spectroscopy and a resting state scan.

We implemented the Tower of London based on a version from a previous study (Lazeron et al., 2000). In the planning condition, two configurations were shown of three colored beads (blue, red, green) placed on three rods that could accommodate 1, 2 or 3 beads, respectively. Subjects had to count the minimum number of moves of beads needed to get from the upper configuration to the lower (Appendix 1). Only a top bead could be moved, and one at a time. Below this setup, two answer options were presented and subjects had to indicate the correct one. In the control condition subjects had to count the number of blue and red beads, as described previously (Lazeron et al., 2000; van den Heuvel et al., 2003). During the resting blocks a fixation cross was shown. The task was presented in a block design consisting of the two alternating task conditions (60 s) interspersed with 30 s resting blocks. The task consisted of 5 blocks of both task conditions. Trials within a block were self-paced and a block was terminated after exactly 60 s. Each trial was interspersed with a 250 ms fixation cross. The task was presented using E-prime 1.2, which logged timing of the task and responses of the subjects. Subjects responded by button presses on an MR-compatible button box using the index and middle finger of their right hand.

Prior to scanning, the task was explained and practiced on a laptop. After explanation, subjects were asked whether the instructions were clear and five trials for the planning condition and 2 for the control condition were presented together with feedback whether the answer was correct. Oral feedback was given when subjects gave an incorrect answer or appeared unconfident about the task instructions. Hereafter, the subjects practiced two planning blocks and one control block of each 1 min that did not include feedback, similar to presentation of the task in the scanner.

2.3. Behavioral measures

To assess apathy we used a data-driven measure of apathy derived from a factor analysis on negative symptoms using the PANSS (Fervaha et al., 2014; Lieburg et al., 2013). These studies resulted in a social amotivation factor that closely resembles apathy: N2 Emotional withdrawal, N4 Apathetic social withdrawal, and G16 Active social avoidance (Cronbach's alpha = 0.75). The correlation between the sum of the PANSS proxy and the Apathy Evaluation Scale total score (AES), an interview to specifically measure apathy (Faerden et al., 2008), is 0.58 (N = 124) in the Faerden sample (courtesy of Ann Faerden, PhD, University of Oslo). To test for associations that may influence the findings of this manuscript, the apathy measures were correlated to age, gender, education, positive symptoms, and haloperidol equivalents (Andreasen et al., 2010).

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