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Negative symptoms in schizophrenia are associated with aberrant striato-cortical connectivity in a rewarded perceptual decision-making task

Greg E. Reckless[a,b,*], Ole A. Andreassen[a,b], Andres Server[c], Tiril Østefjells[a], Jimmy Jensen[a,b,d]

[a] NORMENT — KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
[b] Department of Clinical Medicine, University of Oslo, Oslo, Norway
[c] Department of Neuroradiology, Oslo University Hospital, Oslo, Norway
[d] Centre for Psychology, Kristianstad University, Kristianstad, Sweden

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ABSTRACT

Background: Negative symptoms in schizophrenia have been associated with structural and functional changes in the prefrontal cortex. They often persist after treatment with antipsychotic medication which targets, in particular, the ventral striatum (VS). As schizophrenia has been suggested to arise from dysfunctional connectivity between neural networks, it is possible that residual aberrant striato-cortical connectivity in medicated patients plays a role in enduring negative symptomology. The present study examined the relationship between striato-cortical connectivity and negative symptoms in medicated schizophrenia patients.
Methods: We manipulated motivation in a perceptual decision-making task during functional magnetic resonance imaging. Comparing healthy controls (n = 21) and medicated patients with schizophrenia (n = 18) we investigated how motivation-mediated changes in VS activation affected functional connectivity with the frontal cortex, and how changes in connectivity strength from the neutral to motivated condition related to negative symptom severity.
Results: A pattern of aberrant striato-cortical connectivity was observed in the presence of intact VS, but altered left inferior frontal gyrus (IFG) motivation-mediated activation in patients. The more severe the patient's negative symptoms, the less the connectivity strength between the right VS and left IFG changed from the neutral to the motivated condition. Despite aberrant striato-cortical connectivity and altered recruitment of the left IFG among patients, both patients and healthy controls adopted a more liberal response strategy in the motivated compared to the neutral condition.
Conclusions: The present findings suggest that there is a link between dysfunctional striato-cortical connectivity and negative symptom severity, and offer a possible explanation as to why negative symptoms persist after treatment with antipsychotics.

1. Introduction

Functional magnetic resonance imaging (fMRI) studies have shown that unmedicated patients with schizophrenia (SZ) exhibit reduced activation in the ventral striatum (VS) in response to extrinsic motivation compared to healthy controls (HC) (Juckel et al., 2006b; Nielsen et al., 2012b). It has been suggested that the VS is involved in mediating motivation (Berridge et al., 2009; Knutson et al., 2001) and that dysfunction of the motivation system leads to the symptomology observed in SZ (Barch and Dowd, 2010; Howes and Kapur, 2009; Kapur et al., 2005; Roiser et al., 2009). Both positive (Juckel et al., 2006b; Nielsen et al., 2012b) and negative (Juckel et al., 2006a; Schlagenhauf et al., 2008; Simon et al., 2010; Waltz et al., 2009) symptoms have been associated with abnormal patterns of VS activation. Several studies have reported, however, that motivation-mediated VS activation normalizes after treatment with antipsychotics (Juckel et al., 2006a; Nielsen et al., 2012a) and that the more normal the pattern of activation, the less severe the positive symptoms (Nielsen et al., 2012a). Nevertheless, negative symptoms often persist after treatment with antipsychotics in a sizeable number of patients (Kirkpatrick et al., 2006; Stahl and Buckley, 2007; Tandon et al., 2010).

Negative symptoms are divided into five domains: avolition, anhedonia, asociality and poverty of speech and affect (Kirkpatrick et al., 2006). In patients with schizophrenia these symptoms are associated with poor quality of life (Bow-Thomas et al., 1999; Ho et al., 1998),

* Corresponding author at: NORMENT — KG Jebsen Centre for Psychosis Research, TOP Study, Oslo University Hospital — Ullevaal, Building 49, Kirkeveien 166, Postbox 4956 Nydalen, N-0424 Oslo, Norway. Tel.: +47 98 45 42 63; fax: +47 23 02 73 33.
E-mail address: greg.reckless@medisin.uio.no (G.E. Reckless).

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diminished social functioning leading to long-term morbidity (Dickerson et al., 1999; Milev et al., 2005), impaired interpersonal relationships, and generally poor outcome (Milev et al., 2005). There is a relationship between negative symptom severity and reduced gray (Roth et al., 2004; Sigmundsson et al., 2001) and white (Sanfilipo et al., 2000; Wible et al., 2001) matter volume in the frontal cortex. For example, patients rated high in apathy had reduced bilateral frontal cortical volume compared to HC, while those low in apathy did not (Goghari et al., 2010; Roth et al., 2004). Patients high in negative symptoms also had impaired white matter integrity in the inferior frontal gyrus (IFG) (Wolkin et al., 2003) which suggests that negative symptoms may be associated with dysfunctional connectivity.

Several lines of evidence indicate that SZ may arise from dysfunctional connectivity among neural networks (Friston and Frith, 1995; Fusar-Poli et al., 2010; Lynall et al., 2010; Weinberger et al., 1992). Both resting state fMRI and event-related fMRI have revealed aberrant patterns of connectivity within the cortex (Deserno et al., 2012; Wolf et al., 2009; Woodward et al., 2009) and between the cortex and the basal ganglia network which includes the VS (Salvador et al., 2010; Schlagenhauf et al., 2009; Yoon et al., 2013; Zhang et al., 2012). For example, resting state studies have found hyper-connectivity between the prefrontal cortex (PFC) and portions of the bilateral caudate and putamen (Salvador et al., 2010; Zhang et al., 2012). In contrast, an event-related fMRI study examining reward-processing in unmedicated patients found evidence for reduced fronto-striatal functional connectivity (Schlagenhauf et al., 2009). A similar pattern of hypo-connectivity was also observed in medicated patients during a working memory task (Yoon et al., 2013). This suggests that dysfunctional connectivity may endure after treatment with antipsychotics. Despite the suggestion that striato-cortical connectivity is impaired in schizophrenia, how this connectivity changes when performing cognitive tasks has not been thoroughly investigated. In addition, the relationship between impaired striato-cortical connectivity and negative symptom severity in medicated patients has not been fully explored.

Motivation in SZ is thought to be mediated in part by the VS, the target of antipsychotics (Ginovart and Kapur, 2012), yet a deficit of motivation (avolition) is one of the negative symptoms that involves frontal cortex dysfunction (Goghari et al., 2010; Roth et al., 2004) and can persist in medicated patients (Kirkpatrick et al., 2006; Stahl and Buckley, 2007). A manipulation of motivation can, therefore, be used to explore striato-cortical connectivity and its relationship to negative symptoms in SZ. Motivated, healthy participants have increased VS activation that is proportional to reward magnitude (Engelmann and Pessoa, 2007; Knutson et al., 2001; Reckless et al., 2013). Motivation has been shown to alter how individuals bias their decisions (Henriques et al., 1994; Reckless et al., 2013; Reckless et al., 2014), and the left IFG is involved in mediating the change in bias (Mulder et al., 2012).

The aim of the present study was twofold: 1) identify (motivation-mediated) changes in striato-cortical connectivity in medicated patients with schizophrenia during a cognitive task, and 2) examine the relationship between this connectivity and negative symptom severity. A previously used (Reckless et al., 2014) perceptual decision-making task where individuals had to detect a picture of an animal from among non-animal distracters was employed. Motivation was manipulated using financial incentive. In keeping with previous findings (Juckel et al., 2006a; Nielsen et al., 2012a; Reckless et al., 2013; Reckless et al., 2014) it was hypothesized that both HC and medicated patients would have greater VS activation when motivated. Given the hyper-striato-cortical connectivity observed in patients during resting state fMRI studies (Salvador et al., 2010; Zhang et al., 2012), we hypothesized that SZ patients would exhibit aberrant VS–left IFG connectivity compared to HC. As the left IFG has previously been shown to be involved in adjusting response bias (Rahnev et al., 2011; Reckless et al., 2013; Reckless et al., 2014), it was further hypothesized that altered connectivity between this region and the VS would result in patients with SZ failing to adjust response bias from the motivated to the neutral conditions. In view of the relationship between abnormalities in the frontal cortex and negative symptom severity, and the suggestion that connectivity may play a role, we hypothesized that the more abnormal the connectivity, the greater the negative symptom severity.

2. Methods and materials

2.1. Participants

Twenty-two patients with SZ from both in- and outpatient units across four hospitals in Oslo and twenty-two HC were recruited in accordance with local ethics committee guidelines and gave written, informed consent. Diagnosis was confirmed using the Structured Clinical Interview for DSM-IV-TR Axis I disorders (First et al., 2002) and symptom severity was quantified using the Structured Interview for the Positive and Negative Syndrome Scale — SCI-PANSS (Kay et al., 1987). Items were grouped into the consensus driven five-factor model by Wallwork (Wallwork et al., 2012). Functioning was measured using the Global Assessment of Functioning Scale — split version (GAF (Pedersen et al., 2007)). Inter-rater reliability for these instruments has been previously established in our group (Simonsen et al., 2011). Current IQ was assessed using the two-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 2007), which includes matrix reasoning and vocabulary. Individuals were excluded if they had a history of serious head trauma, somatic/neurological illness, drug or alcohol dependence/abuse in the 3 months prior to testing, or a positive urine drug sample on the day of testing. In addition, HC were excluded if they or a first-degree relative had a serious psychiatric illness. Four patients with SZ and one HC exhibited excessive head motion (>3 mm movement between successive scans) during fMRI acquisition and were excluded. The remaining participants were well matched on demographic variables (Table 1). All patients were medicated [atypical: N = 16 (quetiapine n = 8; olanzapine n = 3; aripiprazole n = 2; risperidone n = 2; clozapine n = 1); typical: N = 2 (chlorprothixene n = 1; perphenazine n = 1)]. Medication was standardized using defined daily dose (DDD) (WHO, 2011). At the time of scanning four patients had

Table 1
Participant demographic data.

	Schizophrenia patients (n = 18)	Healthy controls (n = 21)	Statistical test	Significance (2-tailed)
Gender: male/female	13/5	13/8	$\chi^2(1) = 0.46$	0.50
Age, years	29.2 (9.6)	30.0 (6.1)	$t_{(37)} = 0.33$	0.74
Handedness: right/left	15/3	15/6	$\chi^2(1) = 0.77$	0.40
Education, years	13.6 (2.1)	14.0 (2.6)	$t_{(37)} = 0.47$	0.64
WASI IQ	105 (12)	108 (12)	$t_{(36)} = 0.69$	0.49
PANSS				
Positive	10 (4)			
Negative	11 (4)			
Disorganized	5 (1)			
Excited	5 (1)			
Depressed	9 (3)			
Total	56 (13)			
GAF-S	48 (17)			
GAF-F	51 (13)			
Diagnosis: n (%)				
Paranoid	14 (78)			
Schizoaffective	3 (17)			
Residual	1 (6)			
Duration untreated psychosis: weeks, median (range)	12 (1–500)			
Duration of illness: years[a]	8 (6)			
Psychotic episodes[a]	2 (1)			
Defined daily dose (DDD)	1.1 (1)			

Unless otherwise noted scores represent mean (SD).
[a] n = 16