CORTEX 66 (2015) 35–45

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Research report

Structural and functional dysconnectivity of the fronto-thalamic system in schizophrenia: A DCM-DTI study

Gerd Wagner [a,*], Feliberto De la Cruz [a], Claudia Schachtzabel [a], Daniel Güllmar [b], C. Christoph Schultz [a], Ralf G. Schlösser [a], Karl-Jürgen Bär [a] and Kathrin Koch [c,d]

[a] Department of Psychiatry and Psychotherapy, Jena University Hospital, Germany
[b] Medical Physics Group, Institute of Diagnostic and Interventional Radiology I, Jena University Hospital, Germany
[c] Department of Neuroradiology, Klinikum rechts der Isar, Technische Universität München TUM, Munich, Germany
[d] TUM-Neuroimaging Center of Klinikum rechts der Isar, Technische Universität München TUM, Munich, Germany

ARTICLE INFO

Article history:
Received 31 October 2014
Reviewed 17 December 2014
Revised 20 January 2015
Accepted 11 February 2015
Action editor Peter Kirsch
Published online 2 March 2015

Keywords:
ALIC
DCM
DTI
fMRI
Schizophrenia

ABSTRACT

Evidence suggests that cognitive deficits are a core feature of schizophrenia. The concept of "cognitive dysmetria" has been introduced to characterize disintegration of fronto-thalamic-cerebellar circuitry which constitutes a key network for a variety of neuropsychological symptoms in schizophrenia. The present multimodal study aimed at investigating effective and structural connectivity of the fronto-thalamic circuitry in schizophrenia.

fMRI effective connectivity analysis using dynamic causal modeling (DCM) and diffusion tensor imaging (DTI) were combined to examine cognitive control processes in 38 patients with schizophrenia and 40 matched healthy controls.

Significantly lower fractional anisotropy (FA) was detected in patients in the right anterior limb of the internal capsule (ALIC), the right thalamus and the right corpus callosum. During Stroop task performance patients demonstrated significantly lower activation relative to healthy controls in a predominantly right lateralized fronto-thalamo-cerebellar network. An abnormal effective connectivity was observed in the right connections between thalamus, anterior cingulate and dorsolateral prefrontal cortex. FA in the ALIC was significantly correlated with the thalamic BOLD signal, cognitive performance and fronto-thalamic effective connectivity in patients.

Present data provide evidence for the notion of a structural and functional defect in the fronto-thalamo-cerebellar circuitry, which may be the basis of specific cognitive impairments in schizophrenia.

* *Corresponding author*. Department of Psychiatry and Psychotherapy, Jena University Hospital, Centre for Neuroimaging, Philosophenweg 3, 07743 Jena, Germany.
E-mail address: wagner.gerd@uni-jena.de (G. Wagner).
http://dx.doi.org/10.1016/j.cortex.2015.02.004
0010-9452/

1. Introduction

Schizophrenia is a severe psychiatric disorder characterized by a multitude of symptoms affecting a variety of emotional and cognitive domains. The symptoms themselves have been linked to various brain regions and networks (Goghari, Sponheim, & MacDonald, 2010). Accordingly, the concept of schizophrenia as a dysconnectivity syndrome characterized by disrupted interaction within relevant parts of these networks is gaining increasing acceptance (Andreasen, 1999). In line with this concept, there is mounting evidence in schizophrenic patients of alterations in connectivity within the circuits involved in specific cognitive and emotional processes. Fronto-thalamic feedback loops linking the frontal lobes, the cingulate, the basal ganglia and the thalamus play a critical role in processes such as working memory and cognitive control that are frequently impaired in the context of the disorder (Barch & Smith, 2008; Haber & Calzavara, 2009; Khadka et al., 2013; Woodward, Karbasforoushan, & Heckers, 2012). There is a growing body of evidence that both functional and effective connectivity within these circuits is disrupted in schizophrenia (Dauvermann et al., 2013; Orliac et al., 2013; Schlosser et al., 2003; Wagner et al., 2013; Yan et al., 2009). For instance, Dauvermann et al. (2013) reported a significantly lower thalamo-cortical effective connectivity in high-risk subjects with psychotic symptoms and subjects who subsequently developed schizophrenia. In another recent study (Wagner et al., 2013) we found similar results in terms of a significantly lower bilateral connectivity between the mediodorsal thalamus (MD) and the anterior cingulate cortex (ACC) in patients with schizophrenia compared to healthy volunteers during cognitive control processing as assessed by a Stroop task. This altered effective connectivity was accompanied by structural alterations in the form of white matter volume decreases in the thalamus and the frontal cortex. Alterations in white matter volume and structure are frequently found in schizophrenia. Voxel-based morphometry (VBM) studies and studies using tract-based methods suggest widespread white matter alterations in schizophrenia, predominantly in fronto-temporal areas and diverse specific tracts such as the corpus callosum, the arcuate fasciculus, the cingulate bundle and the internal capsule (Kubicki et al., 2007; Kyriakopoulos, Bargiotas, Barker, & Frangou, 2008). The anterior limb of the internal capsule (ALIC) may be of major relevance, because it comprises fronto-thalamic projections subserving various emotional and cognitive processes known to be impaired in schizophrenia (Levitt et al., 2012; Mamah et al., 2010; Sussmann et al., 2009). Previous studies consistently demonstrated the key role of the dorsal ACC, the DLPFC and the MD in cognitive control (Carter & van Veen, 2007). For these regions aberrant activation patterns in association with deficient behavioral performance were observed in schizophrenia (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). Alterations in core tracts within the fronto-thalamic network such as the internal capsule may play a predominant role in the psychopathology of the disorder and may constitute, in particular, one potential cause for the abnormal connectivity and deficient executive functions.

The association between altered white matter integrity and altered functional or effective connectivity in fronto-thalamic networks has barely been investigated in schizophrenia up to now. In our own study mentioned above we found no correlation between altered white matter structure and altered effective connectivity. In this study white matter structure was assessed with VBM based on anatomical high resolution data which does not allow analysis of specific white matter tracts nor specific diffusivity characteristics such as fractional anisotropy (FA) and may have lower sensitivity to detect specific abnormalities. Therefore, in the present study we used diffusion tensor imaging (DTI) and dynamic causal modeling (DCM) to investigate whether disrupted effective connectivity during cognitive control processing is related to altered white matter connectivity (i.e., altered FA) in patients with schizophrenia. Thus, this project represents a direct extension of our previous work (Wagner et al., 2013). Based on the hypothesis of a direct relationship between altered functional (or, more specifically, effective) and structural connectivity we expected a significant association between alterations in fronto-thalamic connectivity and altered white matter structure in connected white matter fiber tracts (i.e., ALIC, frontal white matter tracts) in schizophrenia.

2. Materials and methods

2.1. *Patients and controls*

A total of 40 patients meeting the DSM-IV criteria for schizophrenia were recruited from the inpatient service of the Department of Psychiatry of the University Hospital Jena. There was no history of drug nor alcohol abuse or dependence in the patient and control groups as assessed using SCID-I. Two patients had to be excluded from the study due to brain abnormalities in the MRI scan.

Thus, the final sample consisted of 38 patients (13 females and 25 males) and 40 healthy control subjects (13 females and 27 males) matched for age and education. Hence, the sample of our previous study (Wagner et al., 2013) was extended by the inclusion of four additional patients and four healthy controls.

On average, patients were 35.8 ± 9.9 years old (age range 22–57 years) and had a mean education of 10.6 ± 1.2 (educational range 8–12 years) years and were not significantly different from the control group (mean age 33.3 ± 8.6, age range 19-55 years, mean education 11.0 ± 1.1 years, educational range 8–12 years).

Patients were on long-term treatment with atypical antipsychotics, for 9.5 years on average. Four patients were being treated with olanzapine, 8 with risperidone, 6 with clozapine, 6 with aripiprazole, 7 with quetiapine and 7 with amisulpride. Five patients were additionally treated with an SSRI.

The patients' psychopathological status was assessed by the Scales for the Assessment of Positive and Negative Symptoms (Andreasen, 1990) (SAPS and SANS). Patients' scores were 39.5 ± 18.8 on SANS and 33.3 ± 26.3 on SAPS. The mean age at onset of schizophrenia was 26.9 years (SD = 9.3). On average, patients had 3.8 episodes with a range of 1–12 episodes.