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White matter pathway organization of the reward system is related to positive and negative symptoms in schizophrenia

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ABSTRACT

The reward system in schizophrenia has been linked to the emergence of delusions on the one hand and to negative symptoms such as affective flattening on the other hand. Previous Diffusion Tensor Imaging (DTI) studies reported white matter microstructure alterations of regions related to the reward system. The present study aimed at extending these findings by specifically investigating connection pathways of the reward system in schizophrenia. Therefore, 24 patients with schizophrenia and 22 healthy controls matched for age and gender underwent DTI-scans. Using a probabilistic fiber tracking approach we bilaterally extracted pathways connecting the ventral tegmental area (VTA) with the nucleus accumbens (NAcc), the medial and lateral orbitofrontal cortices (mOFC, lOFC), the dorsolateral prefrontal cortex (dlPFC) and the amygdala; as well as pathways connecting NAcc with mOFC, lOFC, dlPFC and amygdala resulting in a total of 18 connections. Probability indices forming part of a bundle of interest (PIBI) were compared between groups using independent t-tests. In 6 connection pathways PIBI-values were increased in schizophrenia. In 3 of these pathways the spatial extension of connection pathways was decreased. In schizophrenia patients, there was a negative correlation of PIBI-values and PANSS negative scores in the left VTA–amygdala and in the left NAcc–mOFC connection. A sum score of delusions and hallucinations correlated positively with PIBI-values of the left amygdala–NAcc connection. Structural organization of specific segments of white matter pathways of the reward system in schizophrenia may contribute to the emergence of delusions and negative symptoms in schizophrenia.

1. Introduction

The reward system comprises a network of brain regions including the ventral tegmental area (VTA), the nucleus accumbens (NAcc), the amygdala and prefrontal brain regions such as the medial and the lateral orbitofrontal cortex (mOFC, lOFC) and the dorsolateral prefrontal cortex (dlPFC) (Haber and Knutson, 2010; Sesack and Grace, 2010). It attributes meaning to internal and external stimuli and has therefore been related to the development of delusions in schizophrenia (Heinz and Schlagenhauf, 2010). For instance, neutral stimuli elicit stronger responses in the midbrain and in the ventral striatum in schizophrenia patients compared to healthy controls, which may indicate aberrant attribution of salience to neutral stimuli that could lead to the formation of delusions (Jensen et al., 2008; Romaniuk et al., 2010). Furthermore, the reward system is essential for perceiving pleasure and joy (Haber and Knutson, 2010). Consequently, impairments of the reward system may contribute to negative symptoms such as affective flattening and to deficits in processing rewarding stimuli which have been linked to anhedonia in schizophrenia (Juckel et al., 2006; Strauss, 2013).

Abnormal neuronal connectivity may underlie schizophrenia psychopathology (Friston, 1998). This view has been supported by a series of Diffusion Tensor Imaging (DTI) studies identifying, predominantly, reductions of fractional anisotropy (FA) (Kanaan et al., 2005; Kubicki et al., 2007; Kyriakopoulos et al., 2008). Reduced FA indicates differences in barriers of diffusion and may be related to alterations of fiber orientation or integrity (Jones et al., 2013). Findings of reduced FA in schizophrenia include white matter pathways related to the reward system such as the anterior limb of the internal capsule, the anterior thalamic radiation, the fornix or the uncinate fasciculus (e.g. Skelly et al., 2008; Zhou et al., 2008; Oh et al., 2009; Kubota et al., 2013; Quan et al., 2013).

While most previous studies used region of interest (ROI), voxel based morphometry (VBM), tract based spatial statistics (TBSS) or

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deterministic fiber tracking approaches to analyze diffusion properties such as FA (Kanaan et al., 2005; Fitzsimmons et al., 2013), few groups applied probabilistic fiber tracking methods in schizophrenia (McIntosh et al., 2008; Price et al., 2008; Marenco et al., 2012; Bracht et al., 2013; Kubota et al., 2013). Probabilistic fiber tracking aims at reconstructing the most probable anatomical pathway between regions of interest (ROI) (Behrens et al., 2007). In addition to comparing mean-FA averaged over masks derived from probabilistic fiber tracking maps (Price et al., 2008; Kubota et al., 2013), probabilistic fiber tracking can be used to assess the degree of connectivity between two regions of interest (ROI) (Marenco et al., 2012; Bracht et al., 2013).

It was the aim of our study to specifically investigate white matter connection pathways linking VTA and NAcc with amygdala, OFC and dlPFC using a bilateral probabilistic fiber tracking approach (Kreher et al., 2008). Based on previous DTI findings of structural alterations in schizophrenia, we hypothesized a reduced spatial extension of fiber pathways (Buchsbaum et al., 2006; Levitt et al., 2010; Kubicki et al., 2011; Zalesky et al., 2011; Bracht et al., 2013). Due to the resulting condensation of streamlines, this should be associated with higher probability indices forming part of a bundle of interest (PIBI) (Bracht et al., 2013). Since fMRI studies point to associations of the salience system with positive symptoms such as delusions on the one hand (Jensen et al., 2008; Romaniuk et al., 2010) and to negative symptoms such as emotional withdrawal on the other hand (Juckel et al., 2006; Sorg et al., 2013), we furthermore hypothesized that PIBI-values of clusters which differ between patients and controls would be correlated with Positive and Negative Syndrome Scale (PANSS) scores assessing delusions and anhedonia.

2. Methods

2.1. Subjects

Schizophrenia patients were recruited from the University Hospital of Psychiatry, Bern, Switzerland. Diagnoses were given according to DSM-IV following clinical interview and review of all available case files. Exclusion criteria were history of severe head trauma, substance abuse other than nicotine and neurological disorders. Healthy controls were matched for age, gender and years of education. Additional exclusion criterion for controls was a positive history of psychiatric disorders. All participants were right-handed. The study was approved by the local ethics committee. All participants provided written informed consent. A proportion of schizophrenia patients participated in previous DTI-studies investigating psychomotor retardation (Walther et al., 2011; Bracht et al., 2013). Detailed sample information is given in Table 1.

2.2. Data acquisition

2.2.1. MRI acquisition

All images were acquired with a 12-channel signal reception head coil on a 3-Tesla MR scanner (Siemens Magnetom Trio, Erlangen, Germany). High-resolution T1-weighted MR images were obtained using a 3D Modified Driven Equilibrium Fourier Transform (MDEFT) sequence (Deichmann et al., 2004). The optimized acquisition parameters were as follows: 176 sagittal slices, 256 × 224 matrix (with a non-cubic field of view (FOV) of 256 mm × 224 mm, yielding a nominal isotropic resolution of 1 mm^3), 7.92 ms repetition time (TR), 2.48 ms echo time (TE), 16° flip angle, inversion with symmetric timing (inversion time 910 ms), fat saturation and a12 min total acquisition time. Identical prescription of MR images was achieved using the Siemens autoalign sequence, which automatically sets up consistent slice orientation based on a standard MRI atlas.

2.2.2. Diffusion Tensor Imaging (DTI)

For DTI measurements, we used a spin-echo echo-planar-imaging (EPI) sequence (55 slices, FOV = 256 × 256 mm^2, sampled on a 128 × 128 matrix resulting in 2 mm^3 voxel size, TR/TE = 6000/78 ms) covering the whole brain (40 mT/m gradient, 5/8 partial Fourier, no acceleration factor, bandwidth 1346 Hz/Px). Diffusion-weighted images (DWI) were positioned in the axial plane parallel to the AC–PC line and measured along 42 directions with a b-value = 1300 s/mm^2. The sequence included 4 B0 images without diffusion weighting (the first and every 12th subsequent image). We used a balanced and rotationally invariant diffusion-encoding scheme over the unit sphere to generate the DTI data (Hasan et al., 2001).

2.3. Data analysis

Data were analyzed using Statistical Parametric Mapping (SPM8) (www.fil.ion.ucl.ac.uk/spm), implemented in Matlab 7.6.0 (R2008a; Mathworks, Natick, MA, USA). We used a probabilistic fiber tracking method, which extracts the most probable pathways between two regions of interest (ROI) (Kreher et al., 2008) (www.uniklinik-freiburg.de/mr/live/arbeitsgruppen/diffusion_en.html).

2.3.1. ROIs

Seed point selection was identical to our previous study investigating the medial forebrain bundle in depression (see Supplementary material of Bracht et al., 2014). Regions of interest (ROIs) were selected using the WFU-Pick-Atlas implemented in SPM8 (Maldjian et al., 2003). All ROIs were spatially located in the Montreal Neurological Institute (MNI) space. We chose the following bilateral ROIs: VTA, NAcc,

Table 1
Demographics of schizophrenia patients and healthy controls.
Data are means ± standard deviations. Abbreviations: SZ, schizophrenia; PANSS, Positive and Negative Syndrome Scale, CPZ, chlorpromazine.

Variable	SZ patients (n = 24)		Controls (n = 22)	SZ versus controls
Gender (men)	42%		55%	$Chi^2 = 0.76$, $p = 0.38$[a]
Age (years)	34.5 ± 10.1		40.9 ± 13.5	$T = 1.81$, $p = 0.08$[b]
Years of education	13.1 ± 4.5		14.7 ± 4.2	$T = 1.2$, $p = 0.24$[b]
Paranoid type	15		–	–
Disorganized type	5		–	–
Catatonic type	2			
Residual type	2		–	–
Number of episodes	4.5 ± 6.1		–	–
PANSS total	56.2 ± 17.6		–	–
PANSS positive	12.3 ± 5.1		–	–
PANSS negative	17.1 ± 8.3		–	–
Medication dosage (mg CPZ equivalent)[c]	412 ± 300		–	–
Type of medication (atypical/typical)	Atypical	22	–	
	Both	1	–	

[a] Chi-Square tests were calculated.
[b] Independent t-tests were calculated.
[c] Chlorpromazine equivalents were calculated according to (Woods, 2003).