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Multimodal assessments of the hippocampal formation in schizophrenia and bipolar disorder: Evidences from neurobehavioral measures and functional and structural MRI

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ABSTRACT

A potential clinical and etiological overlap between schizophrenia (SZ) and bipolar disorder (BD) has long been a subject of discussion. Imaging studies imply functional and structural alterations of the hippocampus in both diseases. Thus, imaging this core memory region could provide insight into the pathophysiology of these disorders and the associated cognitive deficits. To examine possible shared alterations in the hippocampus, we conducted a multi-modal assessment, including functional and structural imaging as well as neurobehavioral measures of memory performance in BD and SZ patients compared with healthy controls. We assessed episodic memory performance, using tests of verbal and visual learning (HVLT, BVMT) in three groups of participants: BD patients ($n = 21$), SZ patients ($n = 21$) and matched (age, gender, education) healthy control subjects ($n = 21$). In addition, we examined hippocampal resting state functional connectivity, hippocampal volume using voxel-based morphometry (VBM) and fibre integrity of hippocampal connections using diffusion tensor imaging (DTI). We found memory deficits, changes in functional connectivity within the hippocampal network as well as volumetric reductions and altered white matter fibre integrity across patient groups in comparison with controls. However, SZ patients when directly compared with BD patients were more severely affected in several of the assessed parameters (verbal learning, left hippocampal volumes, mean diffusivity of bilateral cingulum and right uncinated fasciculus). The results of our study suggest a graded expression of verbal learning deficits accompanied by structural alterations within the hippocampus in BD patients and SZ patients, with SZ patients being more strongly affected. Our findings imply that these two disorders may share some common pathophysiological mechanisms. The results could thus help to further advance and integrate current pathophysiological models of SZ and BD.

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1. Introduction

Since the introduction of the Kraepelinian dichotomy which divides major endogenous psychoses into two distinct groups of diseases that are known today as schizophrenia (SZ) and bipolar disorder (BD), this concept has strongly influenced modern psychiatric diagnostic classification systems. However, recent findings have cast doubt on this classification into two separate entities (Craddock and Owen, 2005). Therefore, finding evidence of shared clinical features and/or pathophysiological pathways between these disorders represents a field of great interest in psychiatric neuroscientific research.

Direct comparisons of cognitive and clinical variables revealed that SZ and BD share important clinical and cognitive features (Mann-Wrobel et al., 2011; Schaefer et al., 2013), for example some symptoms of psychosis, memory deficits or affective disturbances. Episodic memory deficits are persistent in both disorders, even in symptom-free intervals (Mann-Wrobel et al., 2011; Schaefer et al., 2013). In BD however, the deficits are usually less severe than in SZ patients (Seidman et al., 2002; Reichenberg et al., 2009).

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In addition to that, some anatomical alterations may be shared across psychosis disorders using multimodal imaging parameters (fibre integrity, volumes, cortical thickness) although the severity of the alterations or the location may be different. For instance, regarding volumetric findings, reduced hippocampal volume has been found frequently in SZ (Wright et al., 2000), but not as consistently in BD (Adler et al., 2007; Koo et al., 2008; Scherk et al., 2008; de Castro-Manglano et al., 2011). This is in line with reports of temporal, occipital and parietal volume and cortical thickness reductions in SZ but not in BD patients in comparison with controls (Rimol et al., 2012). Regarding diffusion tensor imaging (DTI)-studies, current knowledge indicates partly analogical location of fibre integrity (FA) changes in SZ and BD: the recent meta-analysis of (Williamson and Allman, 2012) yielded two regions with significant fibre integrity (FA) changes in SZ: the left frontal deep white matter and the left temporal deep white matter, and a meta-analysis in BD by Vederine et al. (2011) showed two significant right-hemispheric clusters of FA alterations that were located in the parahippocampal gyrus and close to the subgenual anterior cingulate cortex (ACC).

Functional imaging findings in both disorders suggest altered functional connectivity within frontal and between frontal and limbic regions in SZ (Meyer-Lindenberg et al., 2005; Kuhn and Gallinat, 2013) and a frontal–limbic network disturbance in BD (Yurgelun-Todd et al., 2000; Blumberg et al., 2003; Strakowski et al., 2005; Kronhaus et al., 2006; Lyoo and Renshaw, 2010). Current findings in the field of resting-state fMRI support the idea that SZ and BD share core pathophysiological pathways. Resting-state fMRI is an attractive tool because it allows to measure functional activation independently of a specific task. A recent meta-analysis of resting-state studies in SZ showed decreased resting-state activity compared with control subjects in the left hippocampus, the ventromedial prefrontal cortex, the posterior cingulate cortex and the precuneus (Kuhn and Gallinat, 2013). In BD patients, altered functional connectivity between the frontal and the limbic brain (Anand et al., 2009; Chepenik et al., 2010; Ongur et al., 2010; Chai et al., 2011) and between the frontal cortex and the striatum (Anand et al., 2009; Chepenik et al., 2010) has been reported.

In sum, the previous literature thus suggests that both disorders may share deficits in episodic memory and structural abnormalities in the hippocampus, although the results are less consistent in BD compared with SZ. Therefore, in the present study, we combined behavioral testing and structural imaging with resting-state fMRI which allowed us to probe the functional connectivity of the hippocampus with other parts of the brain.

In the current study we investigated the hypothesis that potential shared cognitive symptoms in SZ and BD are directly associated with functional and structural alterations within the hippocampal brain region.

2. Material and methods

2.1. Participants

We included 21 patients with the diagnosis of a paranoid SZ (M [mean] = 38.38 years [SD [standard deviation] = ±10.30]) and 21 patients with the diagnosis of a BD I (mean age: M = 35.67 [SD = ±10.68] years) without any comorbid axis-I or II disorders (including drug abuse) according to the DSM-IV criteria (APA, 1994). We ensured the diagnosis using the Structured Clinical Interview for DSM-

Table 1
Sociodemographic and clinical characteristics and cognitive performance of the SZ patient group (n = 21), the BD patient group (n = 21) and the control group (CON; n = 21). SD and range are in brackets.

	BD	SZ	CON	Statistics
Number	21	21	21	–
Gender f/m	9 f/12 m BD/SZ: χ^2 = 0.18, ns	9 f/12 m SZ/CON: χ^2 = 0.13, ns	8 f/12 m BD/CON: χ^2 = 0.11, ns	χ^2 = Pearson's chi-square
Age (years)	35.67 (10.68)	38.38 (10.30)	36.95 (11.10)	F = 0.34, ns
Education (years)	14.86 (2.43)	15.82 (4.92)	15.85 (1.84)	F = 0.60, ns
Handedness (EHI) L:R	80.75 (18.09)	76.34 (15.65)	80.48 (15.91)	F = −0.45, ns
Duration of illness (yr.)	7.62 (5.82)	8.45 (3.45)	–	t = 0.67, ns
Episodes of illness (nr.)	6.35 (12.00)	4.32 (1.23)	–	t = 0.38, ns
Medication (yr.)	6.26 (6.09)	7.34 (3.78)	–	t = −1.45, ns
Medication categories	21 mood stabilisers 2: addit. antidepressants	21 atypical neuroleptics 5: addi. typical neuroleptics		
Clinical scores				
BDI II	9.85 (8.97)	–	2.10 (3.45)	t = 3.65 **
BRMAS	0.38 (0.25)	–	0.25 (0.44)	t = 0.83, ns
PANSS global	–	63.20 (5.20)	–	–
PANSS positive	–	15.40 (3.00)	–	–
PANSS negative	–	15.11 (1.90)	–	–
PANSS general symptomatology	–	32.60 (4.89)	–	–
Cognitive scores				
HVLT-R (t-scores)	51.27 (12.46)	38.56 (8.14)	56.56 (12.37)	F = 17.76** Post-hoc: CON/BD* CON/SZ** SZ/BD**
BVMT-R (t-scores)	54.91 (8.03)	36.20 (14.61)	54.23 (10.89)	F = 14.89** Post-hoc: CON/BD: ns CON/SZ** BD/SZ**
MWT-B	29.86 (3.31)	28.01 (2.89)	31.96 (2.91)	z = −1.75, ns

Note: ns = non-significant. BDI II = Beck Depression Inventory, BRMAS = Bech Rafaelsen Mania Scale, PANSS = Positive and Negative Syndrome Scale, HVLT-R = Hopkins Verbal Learning Test-Revised [HVLT-R]), BVMT-R = Brief Visuospatial Memory-Test Revised [BVMT-R]), MWT-B = Mehrfachwahl-Wortschatztest, EHI = Edinburgh Handedness Inventory. f = female, m = male.
* $p < 0.01$.
** $p < 0.001$.

IV (SCID-I and SCID-II; German version (Wittchen et al., 1996)) followed by an interview to examine sociodemographic factors. We only recruited remitted patients with BD. We ensured their remitted status by using the diagnostic criteria according to the DSM-IV (Wittchen et al., 1996). Also, we only included BP patients that scored less than 18 points in the German version of the Beck Depression Inventory II (BDI II (Hautzinger et al., 2006)) and less than 7 points in the German version of the Bech Rafaelsen Mania Scale (BRMAS; Bech, 1981).

All patients were treated in the Department of Psychiatry, Goethe-University, Frankfurt, Germany during the time of the experiment. All patients were asked to participate in the current study during their treatment period, and we examined those patients who were willing to participate and who did not fulfil any exclusion criteria. To guarantee a good comparability between the two groups we ensured that the duration of illness (at a minimum of 5 years), the number of episodes of illness and the years of treatment with medication were comparable across disease groups (see Table 1 for further details). All patients had to be in a stable medication status (no significant change) during the last month preceding testing. We also computed chlorpromazine equivalents for each SZ patient using the formula by Woods (2003) and Almeida scores as described by Almeida et al. (2009).

21 healthy participants (mean age: $M = 36.90$ [$SD = \pm 11.06$] years) who were matched with the patient groups in age, gender and education were included in the study. Exclusion criteria for control subjects were current drug-abuse, any kind of neurological disease, a history of psychiatric disorders including axis I and axis II disorders according to DSM-IV (using the SCID I and II (Wittchen et al., 1996)), and an inability to provide informed consent. We ensured that none of the controls had any positive family history of affective or psychotic disorder. Statistical tests (ANOVA, Scheffé post-hoc contrast analyses, chi-square-tests) for differences between the groups regarding age, handedness and parental education revealed no significant group differences (all p-values > 0.05).

The anatomical MRI scans of all participants were reviewed by a neuroradiologist who did not find any clinically relevant pathology. Participants were provided with a description of the study and gave written informed consent before participating. Experimental procedures were approved by the ethical board of the medical department of the Goethe-University, Frankfurt/Main, Germany.

2.1.1. Assessment of cognitive and clinical data

We assessed crystallized intelligence using the MWT-B (Mehrfachwahl-Wortschatz-Test (Lehrl, 2005), the German equivalent of the "Spot-the-Word test"), verbal learning with the Hopkins Verbal Learning Test-Revised [HVLT-R] and non-verbal (visual) learning using the Brief Visuospatial Memory-Test Revised [BVMT-R] (view Table 2 for further details) (all tests taken from the MATRICS test battery (Nuechterlein and Green, 2006)).

We explored the clinical state of the illness across patient groups using disease-specific questionnaires. For SZ patients, the Positive and Negative Syndrom Scale (PANSS (Kay et al., 1987)) was administered. For BD patients, we used the BDI II (Hautzinger et al., 2006) and the BRMAS (Bech, 1981). This was done also for the healthy control group in order to rule out potential affective symptoms.

2.2. Data acquisition

Within 1 week of the diagnostic, cognitive and clinical testing functional and anatomical images were acquired using a Siemens Magnetom Allegra 3 Tesla MRI system (Siemens Medical Systems, Erlangen,

Table 2
A) Post-hoc group comparisons between controls ($n = 21$), SZ patients ($n = 21$) and BD patients ($n = 21$) in the functional connectivity pattern between hippocampus bilaterally and whole-brain functional connectivity. B) Statistical test for group differences regarding the VBM beta scores in the hippocampus left and right (ROIs based on the hippocampus mask total). *T* scores were corrected for multiple comparisons using small volume correction ('svc'). Correction for multiple comparisons using additional FDR correction was noted as 'FDR'. The table only includes significant group comparisons. C) Statistical test for group differences regarding the DTI ROI analysis parameters (FA, MD, RD, L1) regarding the tracts: cingulum, fornix, uncinate fasciculus provided by the JHU White-Matter Tractography Atlas (provided by FSL (Hua et al., 2008)).

ROI mask	Tal. Koord. *x, y, z* (cluster size, voxel)		CON *M (SD)* beta scores	BD *M (SD)* beta scores	SZ *M (SD)* beta scores	F significance	BD>SZ *p*	CON>SZ *p*	CON>BD *p*
A) Resting state: seed hippocampus total									
L. frontal lobe	-19, -27, 26 (506)		0.145 (0.013)	0.034 (0.012)	0.040 (0.015)	$F = 4.41^{*}$	ns	*	*
L. frontal lobe	-21, -47, 25 (475)		0.102 (0.034)	0.056 (0.012)	0.051 (0.043)	$F = 3.23^{*}$	ns	*	*
R. lentiform nucleus	19, -11, 0 (964)		0.071 (0.029)	0.055 (0.018)	0.045 (0.021)	$F = 3.10^{*}$	ns	*	ns
R. putamen	27, 6, 0 (587)		0.092 (0.023)	0.078 (0.018)	0.068 (0.018)	$F = 4.51^{*}$	ns	*	ns
L. thalamus	-3, -6, 0 (617)		0.068 (0.078)	0.061 (0.054)	0.047 (0.056)	$F = 3.18^{*}$	*	*	ns
Bil. para-hippocampal gyrus	-29, -35, -7 (639)		0.081 (0.023)	0.079 (0.025)	0.101 (0.023)	$F=5.42^{**}$	*	*	ns
	31, -21, -12 (885)		0.031 (0.071)	0.042 (0.623)	0.069 (0.653)	$F = 2.99^{*}$	ns	*	ns
Bil. cingulate gyrus	-21, -25, -7 (415)		0.045 (0.034)	0.058 (0.012)	0.078 (0.065)	$F = 6.01^{*}$	ns	*	ns
	16, -19, -3 (338)		0.067 (0.012)	0.080 (0.018)	0.103 (0.065)	$F = 8.67^{*}$	ns	*	ns
B) VBM									
L. hippo-campus	-28, -15, -25 (929)		-0.017 (0.009)	-0.007 (0.009)	0.030 (0.010)	$F = 11.77^{*}$	** (svc) ** (FDR)	** (svc) ** (FDR)	** (svc) p = 0.09 (FDR)
R. hippo-campus	21, -21, -24 (949)		-0.017 (0.04)	-0.007 (0.05)	0.031 (0.05)	$F = 10.89^{*}$ ** (FDR)	** (svc) ** (FDR)	** (svc) ns	ns
C) DTI									
Cingulum	LH	FA	0.408 (0.201)	0.398 (0.023)	0.401 (0.270)	1.78, ns	-	-	-
		MD	0.689 (0.031)	0.705 (0.024)	0.734 (0.029)	16.80^{**}	**	**	*
	RH	FA	0.362 (0.176)	0.357 (0.214)	0.352 (0.263)	2.22, ns	-	-	-
		MD	0.512 (0.041)	0.685 (0.022)	0.609 (0.047)	27.47^{**}	**	**	**
Fornix		FA	0.263 (0.277)	0.245 (0.337)	0.241 (0.341)	5.23^{*}	ns	*	*
		MD	1.458 (0.174)	1.510 (0.154)	1.660 (0.145)	8.38^{**}	ns	**	*
Uncinate fasciculus	LH	FA	0.410 (0.273)	0.420 (0.231)	0.376 (0.035)	17.36^{**}	**	**	ns
		MD	0.732 (0.032)	0.735 (0.081)	0.771 (0.076)	3.69^{**}	p = 0.07	*	ns
	RH	FA	0.353 (0.166)	0.350 (0.268)	0.341 (0.219)	3.71^{*}	p = 0.08	*	ns
		MD	0.726 (0.050)	0.760 (0.083)	0.810 (0.040)	13.32^{**}	**	**	p = 0.10

Note: BA = Brodmann area, TAL = Talairach coordinates, FC = functional connectivity scores, CON = controls, BD = bipolar patients, SZ = schizophrenia patients, FA = fractional anisotropy, MD = mean diffusivity ($mm^2/s \times 10^{-3}$), RD = radial diffusivity ($mm^2/s \times 10^{-3}$), L1 = axial diffusivity ($mm^2/s \times 10^{-3}$).
* $p < 0.01$.
** $p < 0.001$.

Germany) at the Goethe University Brain Imaging Center, Frankfurt am Main, Germany. Each scanning session began with a resting-state functional measurement (echo-planar-imaging [EPI]-sequence, 400 volumes, voxel size: $3 \times 3 \times 3$ mm^3, TR = 2000 ms, TE = 30 ms, 33 slices covering the whole brain, slice thickness = 3 mm, distance factor = 20%, flip angle = 90°), followed by a high-resolution T1-weighted anatomical measurement (MDEFT sequence (Deichmann et al., 2004), 176 slices, $1 \times 1 \times 1$ mm^3). Three diffusion tensor imaging datasets were also acquired for each subject using generalized autocalibrating parallel acquisitions (GRAPPA; Griswold et al., 2002) with an EPI sequence (TR = 8760 ms; TE = 100 ms; bandwith = 1302 Hz/pixel, acquisition voxel size = $2 \times 2 \times 2$ mm^3; 60 axial adjacent slices; slice thickness = 2 mm (no gap); FOV = $192 \times 92 \times 120$ mm; acquisition matrix = 96×96; 10 images without diffusion weighting (b0) with 60 diffusion-encoded images (b-values = 1000 s/mm^2 60 noncolinear directions, acquisition time = 10 min.)).

Participants were scanned with dimmed lights and were instructed to lie still and look at a white fixation cross presented in the centre of the visual field. Participants did not engage in any overt speech during the scanning sequences.

2.3. Image preprocessing: resting-state fMRI

The BrainVoyager QX software version 2.3 (Goebel et al., 2006) was used to preprocess and co-register the functional and anatomical MR images. The preprocessing steps of the functional data included slice-time correction, rigid-body motion correction (Levenberg–Marquardt algorithm; cut-off for head motion: ±2 mm), linear trend removal and high-pass temporal filtering (3 cycles per time course, cutoff = 0.0075 Hz). Three-dimensional (3D) anatomical scans were transformed into Talairach space (Talairach and Tournoux, 1988) using a 12-point affine transformation. We used automated routines of the BrainVoyager software to co-register the functional data to the anatomical scans of the same participant, and resampled the functional data to an iso-voxel size of $3 \times 3 \times 3$ mm^3.

For a seed-based analysis (SBA), we used an anatomically defined hippocampus mask (hippocampus total) provided by the Brain Voyager QX program. The seeds were then used to do a seed correlation analysis (SCA). During SCA, the functional time-series of one or more predefined brain areas (= seed regions) are sampled and correlated with all other functional time-series. Following previous recommendations, we corrected the seed time-series for potential nuisance variables (Z-normalized), which included fMRI signal from ventricles, white matter, the global (whole-brain) signal and the six head movement parameters (Birn et al., 2006; Chai et al., 2012). The analysing steps of the resting-state fMRI data were done with custom-written routines and freely available toolboxes in Matlab (MathWorks, Natick, MA). Results were visualized on the anatomical images using the BrainVoyager QX software.

2.4. Imaging preprocessing: ROI analysis with VBM

The VBM preprocessing and statistical analysis were performed with SPM8 (statistical parametric mapping [Wellcome Department of Imaging Neuroscience, London, UK]) running on MATLAB version 7.7.0. First, all images were checked for artefacts, structural abnormalities and pathologies. Second, customized T1 templates and prior images of grey matter (GM), white matter (WM) and cerebro-spinal fluid (CSF) were created from all participants in order to use it for the group analysis. We used modulated data and prior probability maps (voxel intensity) to guide segmentation in SPM. The segmentation included six different tissue types, light bias regularization (0.001), 60 mm bias FWHM cut-off, warping regularization of 4 mm, affine regularization to the ICBM European brain template (linear registration) and a sampling distance of 3 mm. The quality of the segmentation was checked before further analysis. Finally, the images were smoothed with a Gaussian kernel of $8 \times 8 \times 8$ mm^3 (FWHM). Using this procedure the intensity of each voxel was replaced by the weighted average of the surrounding voxels, in essence blurring the segmented image.

The WFU PickAtlas toolbox in SPM8 (Maldjian et al., 2003) was used to create masks for the left and right hippocampus. The size of the masks was 1000 mm^3 (default). In the following step we compared grey matter volume differences in the ROIs between individual images, using the voxel-based morphometry (VBM) tool of the SPM8 software. Afterwards, group comparisons in the ROIs of GM using VBM were tested with linear statistical contrasts resulting in a *t*-statistic for each voxel. The respective global volumes of grey and white matter and CSF as obtained during segmentation were included as nuisance variables.

2.5. DTI procedures: ROI analysis with FSL

Diffusion MRI data were pre-processed and analysed using the standard TBSS routine of FSL 4.1 (Oxford Centre for Functional MRI of the Brain — FMRIB software library; FSL, http://www.fmrib.ox.ac.uk/fsl) (Smith et al., 2006). TBSS is a specific voxel-wise approach to analyse DTI data, which projects individual DTI parameters of each participant onto a mean skeleton of a white matter mask (Smith et al., 2006). The different steps applied for the preprocessing of the Diffusion MRI data included motion correction, correction for eddy-current distortion and averaging the three DTI datasets into one single-4D dataset per subject. After that, the preprocessed images were fitted using a tensor model that generated the diffusion maps (fractional anisotropy [FA], mean diffusivity [MD]) used in the following TBSS analysis. This was followed by a non-linear registration of all images into standard MNI space and the creation of an averaged FA skeleton on which individual FA and MD values were projected (for further details of the procedure see Oertel-Knöchel et al., 2014). The resulting DTI parameters on the skeleton were used for ROI analyses of all tracts which are connected to the grey matter regions of the hippocampus region. The tracts were selected using the JHU White-Matter Tractography Atlas provided by FSL (Hua et al., 2008). This Atlas tool is recommended by FSL and was used to mark the topographical boundaries of all ROIs in MNI space and to create white matter masks. The tracts were selected as follows: bilateral uncinate fasciculus, bilateral cingulum, fornix.

2.6. Statistical analysis

To generate a two-level general linear model (GLM) (Biswal et al., 1995; Rotarska-Jagiela et al., 2010), we sampled the averaged and normalized (Z-normalization) functional time-series of the predefined seed regions. This resulted in first-level functional connectivity coefficients for each participant. Then, the functional connectivity coefficients of the seed regions were entered into a second-level, mass-univariate one-way analysis of a covariance (ANCOVA) model. In this model the different groups were defined as a between-subject factor while the variables age, sex and education were considered as nuisance covariates. To correct for multiple comparisons, we used the FDR correction for main effect of functional connectivity (thresholded at $p < 0.05$ (Genovese et al., 2002)). The effect of the group factor was then visualized on an anatomical template (courtesy of Montreal Neurologic Institute (MNI)). In a following step, all significant regions on this level were defined as regions-of-interest (ROIs), which were used for a ROI-averaged connectivity analysis (post-hoc, pairwise, two-sample *t*-test [two-tailed]) using voxel functional connectivity coefficients of each participant to assess group contrasts (corrected for multiple comparisons using the cluster-level correction tool ($p < 0.05$; cluster-level correction, minimum cluster size of 200 mm^3)).

The resulting statistical maps of the ROI grey matter analysis using VBM showed all voxels of the ROIs with a significant group difference being set at a (minimum cluster size = 100 mm^3) *p*-value threshold of $p < 0.001$ (small volume correction). The significant results of the analysis are interpreted as volume differences between the groups.

We also computed *t*-tests assessing group differences of ROI FA and MD values (bilateral uncinate fasciculus, fornix, bilateral cingulum) from the DTI analysis (at an alpha set at $p < 0.05$; tfce [threshold free cluster enhancement] corrected), using the SPSS 21.0 software package (Statistical Package for Social Sciences, http://www.spss.com).

Moreover, we performed group comparisons of cognitive measures (BVMT-R, HVLT-R) using two *independent ANOVAs* with group being a fixed factor and the test scores defined as independent variables. Group comparisons of BDI II and BRMAS were conducted using *t*-tests to compare the two groups (BD, CON). All comparisons of cognitive and neurobehavioral measures were conducted with the SPSS 21.0 software package.

We controlled for a potential influence of medication on the results performing a bivariate correlation analysis (Pearson product-moment correlation, two-tailed) between the functional connectivity values and the medication doses computed according to the method by Almeida et al. (2009) for BD patients and chlorpromazine equivalents according to Woods et al. (2003) for SZ patients. In addition, a correlation between the years of medication and the beta values of the functional activation during the resting-state measurement was calculated.

3. Results

3.1. Cognitive and clinical data

Mean (SD) PANSS scores in the group of SZ patients were: global scale: $M = 63.20$ ($SD = \pm 5.20$), positive symptoms: $M = 15.40$ ($SD = \pm 3.00$), negative symptoms: $M = 15.11$ ($SD = \pm 1.90$) and general symptomatology: $M = 32.60$ ($SD = \pm 4.89$) (see Table 1).

Assessing current psychopathology in the groups of healthy control subjects (CON) and of the BD patients, we found that the BDI II scores of the BD patients were significantly higher compared to the control group (BD patients: $M = 9.85$ [$SD = \pm 8.97$], CON: $M = 2.10$ [$SD = \pm 3.45$]; $t = 3.65$, $p = 0.001$) indicating subclinical depressive symptoms in BD patients. BRMAS scores showed no significant group differences (BD patients: $M = 0.38$ [$SD = \pm 0.25$], CON: $M = 0.25$ [$SD = \pm 0.44$]; $t = 0.83$, ns). However, none of the patients or controls fulfilled a score of >18 in the BDI II and a score of >7 in the BRMAS, indicating acute symptoms.

Verbal (HVLT-R) and non-verbal (BVMT-R) learning parameters showed significant group differences across groups (HVLT-R: $F = 17.76$, $p < 0.001$; BVLT-R: $F = 14.89$, $p < 0.001$). Overall, SZ patients showed the lowest values followed by BD patients and controls. The group differences in both memory parameters reached a significant level in the post-hoc contrasts between controls and SZ patients and between BD patients and SZ patients (all *p* values < 0.001). However, the group contrast between controls and BD patients showed significant differences only in the verbal learning values (HVLT; $p < 0.01$). Controls, SZ and BD patients did not differ significantly in crystallized intelligence ($z = -1.75$, ns) (see Table 1).

3.2. Resting-state functional connectivity

The multi-subject result map (voxel-by-voxel one-sample *t*-test of connectivity values) with voxel clusters of significant bilateral *hippocampus total* functional connectivity included left frontal lobe, right lentiform nucleus, right putamen, left thalamus, bilateral parahippocampal gyrus and bilateral cingulate gyrus (ANCOVA, *F*-map corrected for FDR).

3.2.1. Differences between SZ patients and controls

Post-hoc pairwise comparisons (two-sample *t*-tests, corrected for nuisance variables) showed a significant reduction of functional connectivity scores in the left frontal lobe, the right lentiform nucleus, the right putamen and the left thalamus in SZ patients compared with control subjects. Higher functional connectivity scores in SZ patients when compared with controls were found in the bilateral parahippocampal gyrus and in the bilateral cingulate gyrus (all *ps* < 0.001; cluster-level correction; view Fig. 1, Table 2).

3.2.2. Differences between BD patients and controls

Left frontal lobe functional connectivity was also decreased in BD patients in comparison with controls ($p < 0.001$; cluster-level correction; view Fig. 1, Table 2).

3.2.3. Graded differences (CON–BD–SZ)

If graded differences are defined as significant differences between all groups (SZ > BD > CON), none of the functional connectivity parameters fulfilled this criterion. However, in the left thalamus, BD patients showed mean values that lay between controls and SZ patients without showing statistically significant differences in comparison with the control group (view Fig. 1, Table 2).

3.3. VBM results

The VBM ROI analysis of the left and right hippocampus revealed significant differences across groups (left: $F = 11.77$, right: $F = 10.89$, all *ps* < 0.001).

3.3.1. Differences between SZ patients and controls

In the right hippocampal volumes SZ had significantly lower beta scores in comparison with controls. Differences in beta scores in BD as compared to controls did not reach a significant level (CON: $\beta = -0.017$ [SD = ±0.04], BD: $\beta = -0.007$ [SD = ±0.05], SZ: $\beta = 0.031$ [SD = ±0.05]).

3.3.2. Graded differences: CON–BD–SZ

In left hippocampal volumes, controls had the significantly highest beta scores, followed by BD patients and SZ patients (left: CON: $\beta = -0.017$ [SD = ±0.009], BD: $\beta = -0.007$ [SD = ±0.009], SZ: $\beta = 0.030$ [SD = ±0.010]; see Fig. 2, Table 2).

3.4. DTI ROI results

DTI ROI analyses revealed significant group differences in the cingulum bilaterally (MD), in the fornix (FA, MD) and the uncinate fasciculus bilaterally (FA, MD) (all *p*; tfce < 0.05).

3.4.1. Differences in both patient groups in comparison with controls

Scheffé post-hoc single contrasts for the left and right cingulum showed the lowest values for MD in controls (all *p* (tfce) < 0.05). Post-hoc group comparisons between the two patient groups showed significantly higher MD scores in SZ than in BD patients in the left cingulum, and – the other way around – for the right cingulum (highest MD scores in BD) (all *p* (tfce) < 0.05).

After computing post-hoc single contrasts of the fornix we found significantly lower FA/higher MD values for both patient groups in comparison with controls (*p* (tfce) < 0.05), but no significant group contrast between the patient groups (*p* (tfce) > 0.05).

3.4.2. Differences between SZ patients and controls

In the left and right uncinate fasciculus, SZ patients showed lower FA values in comparison with controls ($p < 0.001$).

3.4.3. Graded differences: CON–BD–SZ

A comparison of MD values in the bilateral uncinate fasciculus resulted in higher values in controls as compared to SZ patients (all *ps* (tfce) < 0.05). BD patients showed trend level significance in the MD scores of the right uncinate fasciculus compared with controls ($p = 0.10$). Furthermore, in computing a direct comparison between the two patient groups, MD scores of the right uncinate fasciculus proved to be significantly increased in SZ patients in comparisons with BD patients. There was also trend level significance in the MD scores of the

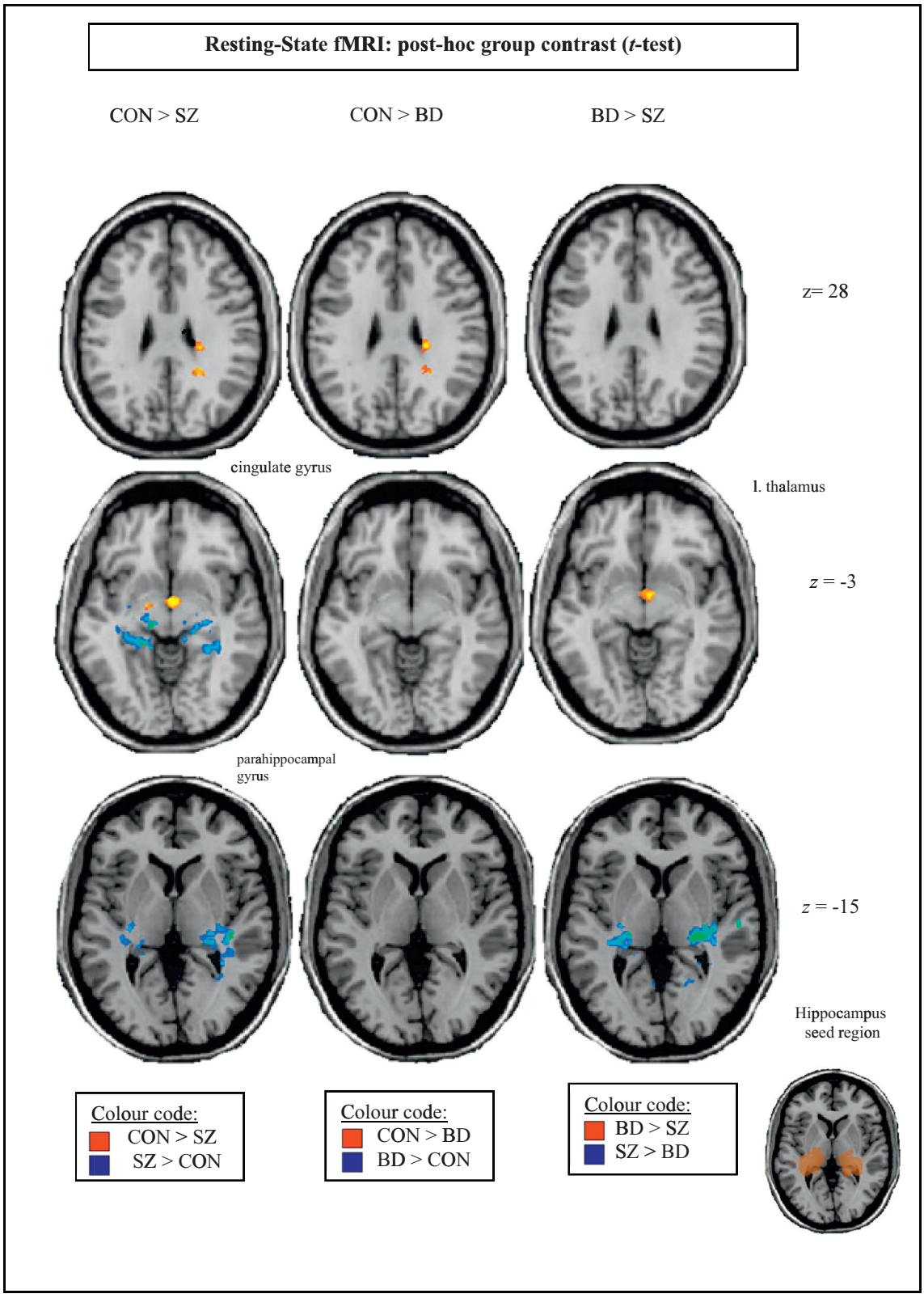

Fig. 1. Post-hoc comparisons (*t*-tests) of the functional connectivity between CON > SZ, CON > BD and BD > SZ (t-map cluster-level corrected, $q < 0.05$). Regions indicating significant group differences with hippocampus total as seed-region. CON = controls, BD = bipolar patients, SZ = schizophrenia. The left side in the figure indicates the right side of the brain (radiological convention). Colour codes: contrast CON > SZ: red = higher functional connectivity scores in controls, blue = lower functional connectivity scores in controls (compared with SZ patients). Contrast CON > BD: red = higher functional connectivity scores in controls, blue = lower functional connectivity scores in controls (compared with BD patients). Contrast BD > SZ: red = higher functional connectivity scores in BD patients, blue = lower functional connectivity scores in BD patients (compared with SZ patients).

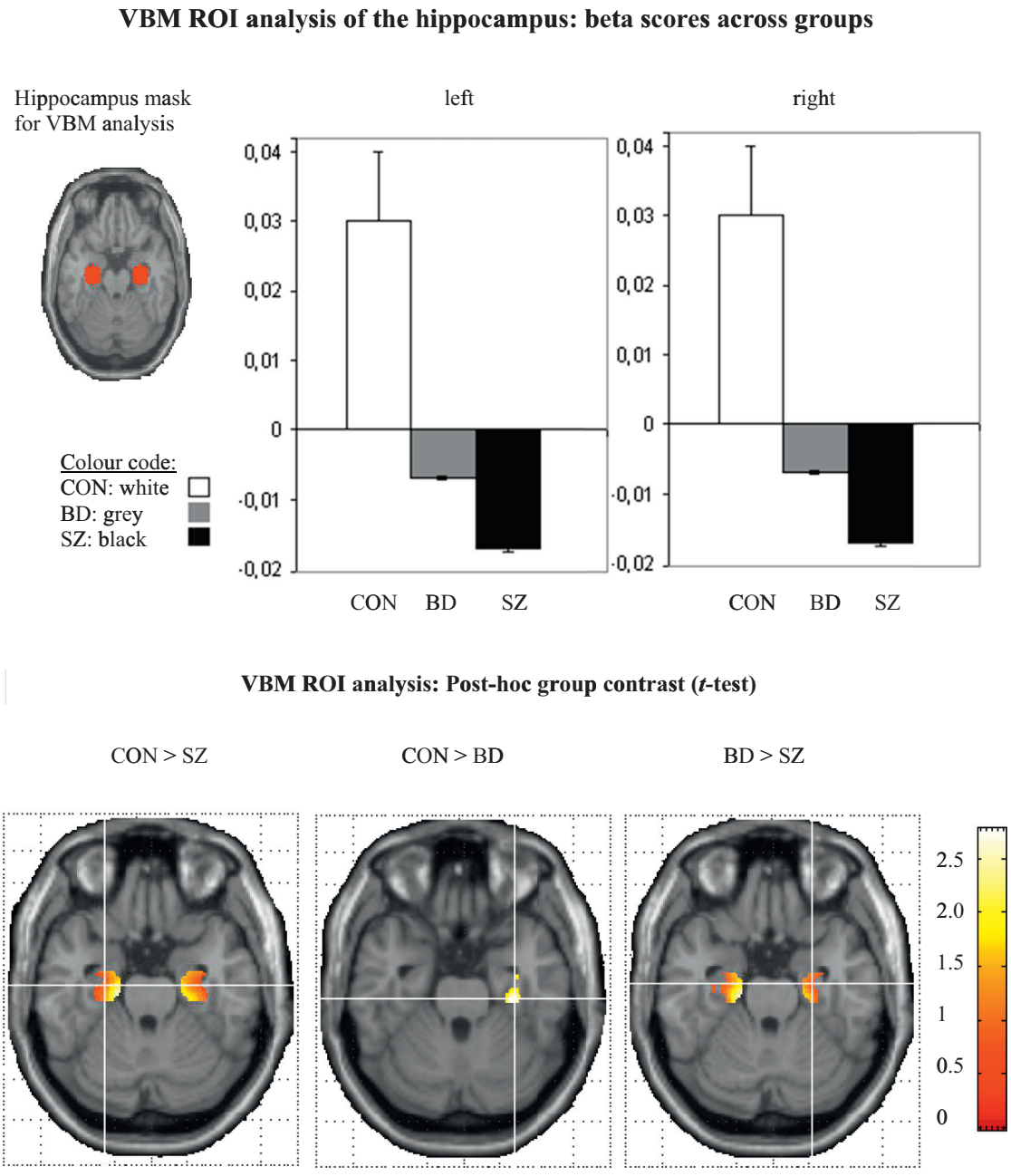

Fig. 2. Upper row: One-way ANCOVA (*F*-test fitted response) of the beta scores of the ROI VBM analysis of the hippocampus with group as between-subject factor and age, sex and education as covariates. Middle row: Beta scores across groups of left and right hippocampus across groups (colour code: white = CON, grey = BD, black = SZ). Lower row: *T*-tests of the group contrasts CON > SZ, CON > BD and BD > SZ (statistical threshold: *q* [small volume correction] < 0.001). The left side in the figure indicates the right side of the brain (radiological convention).

left uncinate fasciculus and the FA scores of the right uncinate fasciculus between SZ and BD patients ($p < 0.10$) (see Fig. 3, Table 2).

3.5. Correlation analyses

None of the clinical parameters separately assessed for each disease group (positive and negative symptoms in SZ [PANSS], acute affective symptoms [BDI II for depressive, BRMAS for manic symptoms]) showed a significant correlation with any of the functional or structural imaging parameters (all p values > 0.05).

The BVMT-R (non-verbal learning) values were not significantly associated with any of the imaging parameters across groups ($p > 0.05$). Verbal learning, however (measured using the HVLT-R) was significantly correlated with right hippocampus volumes in the BD ($r = 0.490$, $p = 0.03$) and in the SZ ($r = 0.395$, $p = 0.04$) patient groups (but not in controls; $p > 0.05$). Yet these correlations did not reach significance after correcting for multiple comparisons (Bonferroni correction).

None of the imaging parameters showed any significant correlation with the medication scores or with years of medication in BD or SZ patients ($p > 0.05$).

4. Discussion

4.1. Resting-state functional connectivity

Our seed-based functional connectivity analysis (resting-state fMRI) with the bilateral hippocampus as the seed region revealed markers of hypo- and hyperconnectivity between hippocampal and fronto-limbic

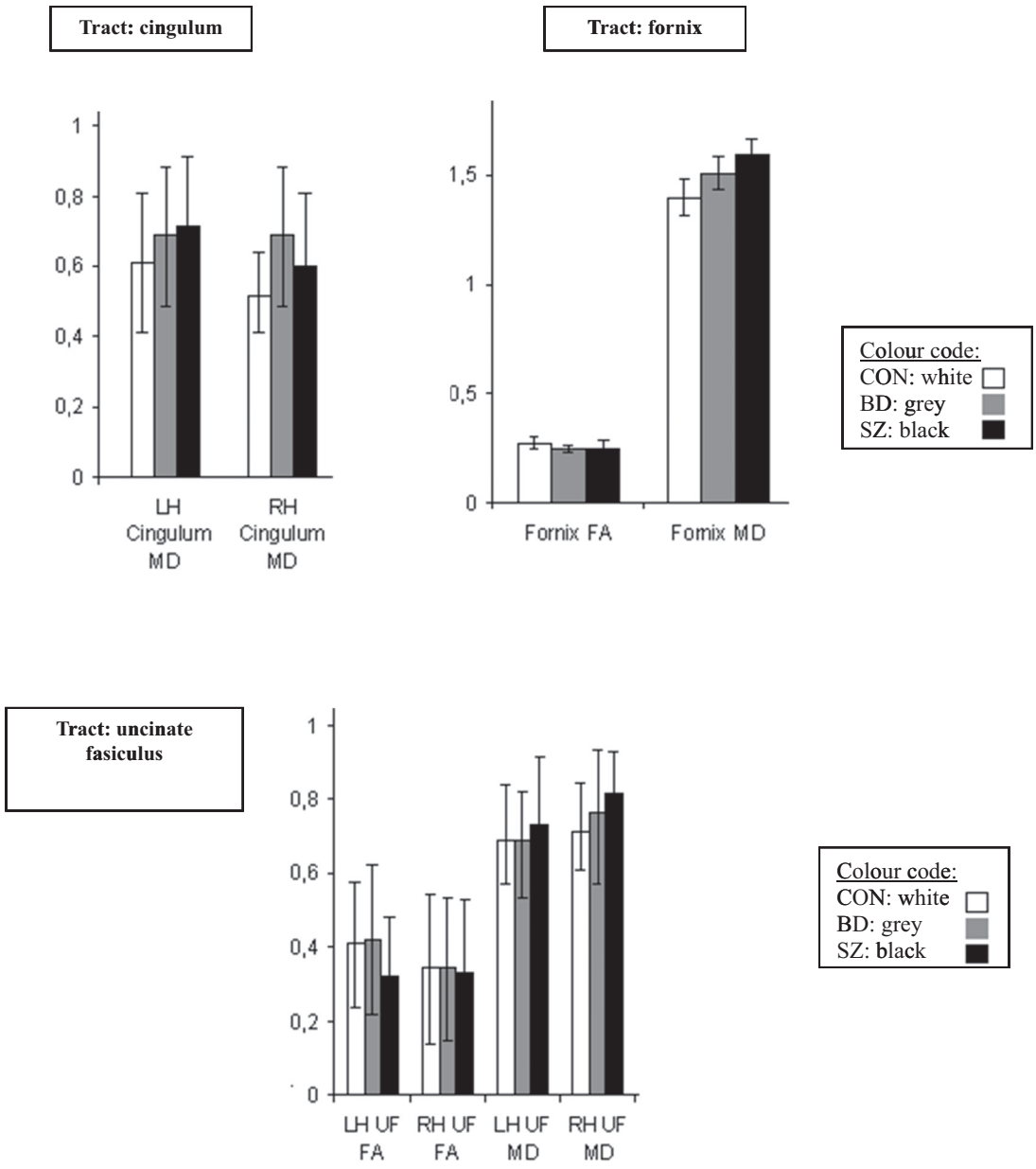

Fig. 3. Group comparisons in DTI ROI analyses, regarding the tracts cingulum (left and right, upper row), fornix (middle row) and uncinate fasciculus (left and right, lower row), with group as between-subject factor and FA, MD, RD and L1 scores as independent variables. Only those values which deemed significant during group comparisons have been shown here. Colour code: CON = black, BD patients (BD) = grey, SZ patients (SZ) = white.

regions in both, SZ and BD patients, when compared with controls. In particular, SZ patients showed hypoconnectivity between the bilateral hippocampus, the left frontal lobe, the left thalamus, the bilateral lentiform nucleus and the right putamen. The results confirm current neurophysiological models that suggest altered functional connectivity within frontal and between frontal and limbic regions in SZ (Meyer-Lindenberg et al., 2005; Kuhn and Gallinat, 2013) and a frontal–limbic network disturbance in BD (Yurgelun-Todd et al., 2000; Blumberg et al., 2003; Strakowski et al., 2005; Kronhaus et al., 2006; Lyoo and Renshaw, 2010). Accordingly, current resting-state findings in BD patients revealed changes in the functional connectivity between frontal and limbic brain regions in comparison with controls (Anand et al., 2009; Chepenik et al., 2010; Ongur et al., 2010; Chai et al., 2011) and fronto-striatal hypoconnectivity during rest in BD patients (Anand et al., 2009; Chepenik et al., 2010).

Moreover, SZ patients showed higher functional connectivity scores in the bilateral parahippocampal gyrus and in the bilateral cingulate gyrus when compared with control subjects. The findings of disturbed connectivity in a fronto-limbic network with both – hypo- and hyperconnectivity in SZ patients – are in line with the theory of a disconnectivity syndrome in psychiatric disorders first proposed by Friston (1998) that suggested a failed connectivity between relevant brain regions. The result of either increased or decreased functional connectivities between the hippocampus and fronto-limbic brain regions shows the complex pattern of disturbance of brain networks in SZ. Furthermore, our findings in BD patients are in accordance with a recent meta-analysis (e.g., (Chen et al., 2011)) which mainly suggests hyperactivity of limbic regions but not directly of the hippocampus in BD patients.

4.2. Volumetric (VBM) findings

Both SZ and BD patients showed lower grey matter volumes in the left hippocampus in comparison with controls; however volume deficits

in the right hippocampus were limited to SZ patients. This is in-line with previous findings, which robustly show hippocampal volume reductions in SZ (Wright et al., 2000), but only inconsistently in BD (Adler et al., 2007; Koo et al., 2008; Scherk et al., 2008). Our findings therefore confirm the hypothesis of Brown et al. (2011) that hippocampal volume may be of importance for the differentiation between SZ and BD. Brown and colleagues based their assumption on direct comparisons of grey matter volumes in subcortical regions, showing lower volumes in SZ patients compared with BD patients in the right hippocampus, in the putamen and the amygdala.

4.3. White matter fibre integrity/mean diffusivity (DTI)

White matter fibre integrity, as assessed by mean diffusivity, was strongly affected in SZ patients in the tracts connecting the hippocampus with other brain structures (uncinate fasciculus, cingulum, fornix), whereas alterations in the BD patients were more subtle. This result is in line with findings of multiple white matter changes in SZ including the interconnections of the frontal lobe, thalamus, cingulate gyrus and white matter changes of the left temporal deep white matter (interconnections of frontal lobe, insula, hippocampus-amygdala, temporal lobe, occipital lobe) (Williamson and Allman, 2012). Accordingly, in BD patients, mainly right-sided changes in DTI parameters have been reported (parahippocampal gyrus and close to the subgenual ACC) (Vederine et al., 2011).

4.4. Graded differences: CON–BD–SZ

Overall, the current data partly support the concept of graded changes across the SZ and BD spectrum. SZ patients show more pronounced deficits regarding neurobehavioral measures of episodic memory performance, alongside with stronger structural alterations when compared with BD patients. BD patients showed more subtle behavioral deficits in memory performance, and also more subtle functional and structural changes in comparison with controls. In a direct comparison, visual learning (HVLT), left hippocampal volume (VBM), mean diffusivity of the bilateral cingulum and the right uncinate fasciculus showed evidences for the idea that both patient groups are affected, but BD patients less severe. However, the resting state functional connectivity and other anatomical parameters did not support this concept of graded change.

The main finding of graded changes across the SZ and BD spectrum can be interpreted as partly contradictory to Kraepelin's (Kraepelin, 1896) distinction of two entirely different and independent disease entities. However, our findings are in line with a large body of recent imaging and genetic research showing that BD and SZ share some core molecular and pathophysiological mechanisms (Craddock and Owen, 2005; Craddock and Owen, 2010) and thereby cannot be conceptualized as two entirely distinct classes of disorders. We may assume that BD and SZ may share some pathophysiological pathways but that there might be also distinct alterations across multimodal measures. Such an interpretation would conform with the findings from recent genome-wide association studies, which reveal partial but not complete overlap of the genetic risk profiles of these disorders (Hall et al., 2014).

4.5. Imaging parameters without graded changes

Resting-state analysis revealed reduced functional connectivity in the left frontal lobe, the right lentiform nucleus, the right putamen and the left thalamus in SZ patients compared with control subjects, and higher functional connectivity scores in SZ patients when compared with controls in the bilateral parahippocampal gyrus and in the bilateral cingulate gyrus, but no alterations in BD patients. In contrast, left frontal lobe functional connectivity was decreased in BD patients in comparison with controls but not in SZ patients. Right hippocampal volumes might not be affected in BD patients but in SZ patients in comparison with controls. Regarding DTI parameters, mean diffusivity (MD) of fibre tracks related to the hippocampus showed graded changes, but this was less present in fibre integrity parameters (FA).

4.6. Cognitive and clinical data in association with imaging findings

Clinical parameters specifically assessed for each disease group separately revealed no significant associations with the imaging findings. That means that our main findings are independent of acute symptomatology, including positive and negative symptoms in SZ [PANSS], and acute affective symptoms (BDI II for depressive, BRMAS for manic symptoms) in BD patients. However, our study was neither powered nor specifically designed to assess such correlations because our patient samples showed relatively low severity scores of acute symptoms.

Verbal learning (HVLT-R) scores showed significant group differences across groups, with the lowest values found for SZ patients and subtle deficits in BD patients in comparison with healthy controls. Crystallized intelligence did not differ across groups, and all main group differences in imaging parameters were independent of crystallized intelligence. Furthermore, verbal learning (HVLT-R) was significantly correlated with right hippocampal volumes in the BD and in the SZ patient groups although these comparisons did not last after correcting for multiple comparisons.

4.7. Limitations

Although all patients of our study were treated with psychiatric medication at the time of measurement, we tested potential influence of psychiatric medication on the functional and structural brain changes in our study. We failed to show any association between functional and structural parameters and medication status or duration of medication use. This result confirms previous findings that report no influence or even a positive effect (reduced group differences between patients and controls) of psychopharmacological treatment on structural and functional findings in psychiatric patients (Dazzan et al., 2005; Hafeman et al., 2012).

The sample size of the current study is relatively small, but we ensured that all patients were screened applying very strict inclusion criteria. For instance, we included only BD patients with BD I disorder (not BD II), we included only SZ patients with paranoid subtype (no schizoaffective or other subtype), and we ensured that none of the patients had any history of drug addiction.

5. Conclusions

A direct comparison of SZ and BD, two major psychotic disorders, is of interest regarding the ongoing debate that was started with the introduction of the Kraepelinian dichotomy concept in 1896 (Kraepelin, 1896). Currently this debate centres on the question whether BD and SZ are distinct disorders or may share some pathophysiological pathways. Our research suggests that although both examined patient-groups may share some pathophysiological pathways, functional and structural abnormalities may be more severe in SZ than in BD. Further studies are needed to explore and explain these graded changes in SZ and BD to define which parameters show graded changes and which do not.

The approach to examine functional as well as structural markers in the same study follows recent developments in the field (Womer et al., 2009), suggesting a mechanistic relationship between structural and functional abnormalities. Thus, the development of a multi-modal neurophysiological model of psychoses, with shared and distinct pathways across traditional disease entities, may help to clarify the

pathways that contribute to individual symptom patterns (Linden, 2012).

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