BRAIN
A JOURNAL OF NEUROLOGY

Aberrant topology of striatum's connectivity is associated with the number of episodes in depression

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In major depressive disorder, depressive episodes reoccur in ~60% of cases; however, neural mechanisms of depressive relapse are poorly understood. Depressive episodes are characterized by aberrant topology of the brain's intrinsic functional connectivity network, and the number of episodes is one of the most important predictors for depressive relapse. In this study we hypothesized that specific changes of the topology of intrinsic connectivity interact with the course of episodes in recurrent depressive disorder. To address this hypothesis, we investigated which changes of connectivity topology are associated with the number of episodes in patients, independently of current symptoms and disease duration. Fifty subjects were recruited including 25 depressive patients (two to 10 episodes) and 25 gender- and age-matched control subjects. Resting-state functional magnetic resonance imaging, Harvard-Oxford brain atlas, wavelet-transformation of atlas-shaped regional time-series, and their pairwise Pearson's correlation were used to define individual connectivity matrices. Matrices were analysed by graph-based methods, resulting in outcome measures that were used as surrogates of intrinsic network topology. Topological scores were subsequently compared across groups, and, for patients only, related with the number of depressive episodes and current symptoms by partial correlation analysis. Concerning the whole brain connectivity network of patients, small-world topology was preserved but global efficiency was reduced and global betweenness-centrality increased. Aberrant nodal efficiency and centrality of regional connectivity was found in the dorsal striatum, inferior frontal and orbitofrontal cortex as well as in the occipital and somatosensory cortex. Inferior frontal changes were associated with current symptoms, whereas aberrant right putamen network topology was associated with the number of episodes. Results were controlled for effects of total grey matter volume, medi-

cation, and total disease duration. This finding provides first evidence that in major depressive disorder aberrant topology of the right putamen's intrinsic connectivity pattern is associated with the course of depressive episodes, independently of current symptoms, medication status and disease duration. Data suggest that the reorganization of striatal connectivity may interact with the course of episodes in depression thereby contributing to depressive relapse risk.

Introduction

Major depressive disorder is one of the most frequent psychiatric disorders with a lifetime prevalence of ~16% (Kessler et al., 2003). Major depression is characterized by single or recurrent major depressive episodes, which include depressed mood, reduced energy, impaired cognition, vegetative symptoms, and suicidal tendency with suicide rates of 4% (American Psychiatric Association, 2000). In 35–85% of cases the course of major depression includes the recurrence of depressive episodes (Hardeveld et al., 2010; Lewis et al., 2010; Farb et al., 2011). However, our knowledge about factors and mechanisms contributing to episode relapse is only fragmentary.

Depressive episodes are associated with widespread structural and functional brain changes (Greicius et al., 2007; Erk et al., 2010; Sheline et al., 2010; Aizenstein et al., 2011; Lui et al., 2011; Li et al., 2012; Mwangi et al., 2012; Zeng et al., 2012; for review Savitz and Drevets, 2009; Hamilton et al., 2012; Whitfield-Gabrieli and Ford, 2012). For example, aberrant resting-state functional connectivity, which has been proved to separate patients from healthy control subjects by pattern classification, was found in the default mode network, salience network, occipital areas, subcortical areas and the cerebellum (Zeng et al., 2012). Particularly, connectivity changes in the default mode and salience networks, which are both intrinsic networks of synchronous ongoing activity (Greicius et al., 2007; Seeley et al., 2007), have been linked with patients' impaired self-focused processing and aberrant emotional reactivity (Sheline et al., 2010; Hamilton et al., 2011, 2012; Whitfield-Gabrieli and Ford, 2012). These widespread functional brain changes, which are detectable even during rest, indicate altered large-scale organization of intrinsic brain activity in depressive episodes. Graph-based network analysis allows us to map such brain organization changes by quantifying topological properties of functional networks consisting of nodes (i.e. brain regions) and edges (i.e. functional connectivity between regions) (Bullmore and Sporns, 2009). Using resting-state functional MRI and graph-based methods, Zhang et al. (2011) found aberrant global efficiency of the whole brain intrinsic functional connectivity network as well as changed nodal centrality of specific brain regions' connectivity in patients with first depressive episode. Such aberrant topology of connectivity during episodes is modulated by early life experience such as childhood neglect (Wang et al., 2013), and its modularity (i.e. the organization in ensembles of regions with strong within-module functional connectivity) is distinctively changed depending on whether patients suffer

from their first or long-term therapy resistant episode (Tao et al., 2013). Because of these findings we hypothesized that specific changes of the topology of intrinsic connectivity, particularly those reflecting functional integration (i.e. efficiency, centrality or modularity), may interact with the course of major depression.

Besides sub-depressive residuals, the number of previous depressive episodes has strongest influence on the course of major depression (Kendler et al., 2001; Hardeveld et al., 2010; Moylan et al., 2013). A recent meta-analysis demonstrated the number of episodes to be one of the best predictors for the episode relapse risk in major depression (Hardeveld et al., 2010). However, it remains poorly understood which neural mechanisms might contribute to such relationship (Robinson and Sahakian, 2008). Because of the course-sensitive aberrant topology of brain connectivity during episodes, we hypothesized that selective changes of intrinsic connectivity, which reflect altered functional integration, interact with the course of episodes in major depression. In more detail, we aimed to address the question whether and how the topology of intrinsic functional connectivity is related to the number of episodes in patients with recurrent major depression, independently of current symptoms and the total duration of the disease.

Therefore, patients with recurrent major depression and healthy control subjects were assessed by resting-state functional MRI and graph-based analysis. Resting-state blood oxygenation level-dependent signal fluctuations were used as a surrogate for intrinsic brain activity (Fox and Raichle, 2007; Raichle, 2010). Graph-based topological scores were restricted to measures of functional integration (i.e. estimates reflecting the efficiency of the interaction between distributed brain areas) and centrality (i.e. degree and betweenness-centrality both reflecting the importance of nodes for functional integration) (Rubinov and Sporns, 2010). We used the Harvard-Oxford brain atlas and functional connectivity across regions to determine each subject's functional connectivity matrix. Topological scores were derived from these matrices, compared across groups and, in patients only, related to the number of depressive episodes and current depressive symptoms by partial correlation analysis. Because of previous findings that demonstrate a link between structural changes and the course of major depression (Sheline et al., 1999; MacQueen et al., 2003; Frodl et al., 2008; Kronmuller et al., 2009), we controlled analyses for structural changes. In addition, effects of medication, disease duration, and accumulated stress, which may interact with the course of depression (Robinson and Sahakian, 2008; Hardeveld et al., 2010), were controlled.

Materials and methods

Subjects

Twenty-five patients with recurrent major depression (two to 10 depressive episodes; mean age of 48.8 years; 13 female) and 25 healthy persons (mean age of 44.0 years; 14 female) participated in this study (Table 1). All participants provided informed consent in accordance with the Human Research Committee guidelines of the Klinikum rechts der Isar, Technische Universität München. Patients were recruited from the Department of Psychiatry by treating psychiatrists, healthy control subjects from the area of Munich by word-of-mouth advertizing. Participants' examination included medical history, psychiatric interview, and psychometric assessment. Psychiatric diagnoses were based on Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV; American Psychiatric Association, 2000). The Structured Clinical Interview for DSM-IV (SCID) was used to assess the presence of psychiatric diagnoses (Spitzer *et al.*, 1992). Severity of clinical symptoms was measured with the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960). The global level of social, occupational, and psychological functioning was measured with the Global Assessment of Functioning Scale (Spitzer *et al.*, 1992). Psychiatrists D.S. and M.S. performed clinical-psychometric assessment; they have been professionally trained for SCID interviews with inter-rater reliability for diagnoses and scores of $>95\%$.

Recurrent major depression was the primary diagnosis for all patients. Patients with recurrent major depression constitute a heterogeneous clinical group, varying in severity of current symptoms, age of disorder onset, duration of the disorder, number of depressive episodes, family history of major depression, co-morbidity of other disorders, and type of medication. Since the goal of the present study was to determine the relationship between the topology of the brain's functional connectivity network and the course of major depression common to most patients with recurrent major depression, we adopted selection criteria from a previous study on recurrent major depression to obtain a clinically representative patient sample (Hennings *et al.*, 2009). Recurrence implies the return of an entirely new episode after clinical recovery. Due to the unreliable self-report in major depression because of patients' potential memory problems, the determination of episode number was based on the review of patients' medical records. Only patients whose records enabled us to determine a consistent episode number were included in the study. The number of episodes of all patients ranged from two to 10 following a continuous distribution (Supplementary Fig. 1). All patients met criteria for a current depressive episode with an average episode length of 16.6 weeks [standard deviation (SD) 6.6] and an averaged HAM-D score of 22 (SD 7.1). The average age of major depression onset was 32 years (SD 8), and all patients experienced their first episode before 45 years of age. The average duration of major depression was 16.7 years (SD 10.2) and on average, patients had experienced five to six episodes (mean 5.6, SD 2.5). On average 1.7 episodes (SD 1.1) were triggered by stressful life events; episodes triggered by a stressful life event were defined as episodes that started within 1 month after a stressful life event. Four patients had a positive family history of major depression. Fourteen patients had psychiatric co-morbidities: six generalized anxiety disorder, three somatization disorder, and five avoidant or dependent personality disorders. Patients with psychotic symptoms, schizophrenia, schizoaffective disorder, bipolar disorder, and substance abuse were excluded from this study. Additional exclusion criteria were pregnancy, neurological or severe internal systemic diseases, and general contraindications for MRI. One patient was free

Table 1 Demographic, clinical and psychometric data

	Patients with major depression	Healthy controls	*P*-value
Subjects [total number]	25	25	
Age [years]	48.76 (14.83)	44.08 (14.78)	>0.05
Gender	13F/12M	14F/11M	>0.05
Number of episodes	5.6 (2.5)	NA	
Duration of major depression [years]	16.7 (10.2)	NA	
Current episode			
Duration [weeks]	16.6 (6.6)	NA	
HAM-D	22 (7.1)	0	<0.001
GAF	50 (10.5)	99.5 (1.1)	<0.001

Group comparisons: two-sample *t*-tests for age, HAM-D, and GAF; χ^2-test for gender. Data are presented as mean and SD (in brackets). GAF = Global Assessment of Functioning.

of any psychotropic medication during MRI assessment. Seven patients were treated by antidepressant mono-therapy [three cases: citalopram 30 mg/d (mean dose); three cases: sertraline 200 mg/d; one case: mirtazapine 30 mg/d]; 12 patients by dual-therapy (five cases: citalopram 37.5 mg/d + mirtazapine 30 mg/d; two cases: citalopram 40 mg/d + venlafaxine 225 mg/d; one case: citalopram 30 mg/d + quetiapine 200 mg/d; one case: sertraline 200 mg/d + mirtazapine 30 mg/d; three cases: venlafaxine 225 mg/d + mirtazapine 30 mg/d); and five patients by triple-therapy (two cases: citalopram 30 mg/d + venlafaxine 187.5 mg/d + amisulprid 200 mg/d; two cases: citalopram 30 mg/d + mirtazapine 30 mg/d + quetiapine 200 mg/d; 1 case: venlafaxine 22 mg/d + mirtazapine 30 mg/d + quetiapine 200 mg/d). All healthy control subjects were free of any current or past neurological or psychiatric disorder or psychotropic medication.

Data acquisition and preprocessing

All participants underwent 10 min of resting-state functional MRI with the instruction to keep their eyes closed and not to fall asleep. We verified that subjects stayed awake by interrogating via intercom immediately after the resting-state functional MRI scan. No patient dropped out during the scanning session.

Data acquisition

MRI was performed on a 3 T MR scanner (Achieva, Philips) using an 8-channel phased-array head coil. For co-registration and volumetric analysis, T_1-weighted anatomical data were obtained by using a MP-RAGE sequence (echo time = 4 ms, repetition time = 9 ms, inversion time = 100 ms, flip angle = $5°$, field of view = $240 \times 240 \, mm^2$, matrix = 240×240, 170 slices, slice thickness = 1 mm, and 0 mm interslice gap, voxel size = $1 \times 1 \times 1 \, mm^3$). Functional MRI data were obtained by using a gradient echo EPI sequence (echo time = 35 ms, repetition time = 2000 ms, flip angle = $82°$, field of view = $220 \times 220 \, mm^2$, matrix = 80×80, 32 slices, slice thickness = 4 mm, and 0 mm interslice gap, voxel size = $2.75 \times 2.75 \times 4 \, mm^3$; 300 volumes).

Preprocessing

The first three functional images of each subject's data set were discarded because of magnetization effects. The remaining resting-state functional MRI data were preprocessed by SPM8 (Wellcome Department of Cognitive Neurology, London) including head motion correction, spatial normalization into the standard stereotactic space of

the Montreal Neurological Institute with isotropic voxel of $3 \times 3 \times 3 \, mm^3$, and spatial smoothing with a $6 \times 6 \times 6 \, mm^3$ Gaussian kernel to reduce spatial noise. To ensure data quality, particularly concerning motion-induced artefacts, temporal signal-to-noise ratio and point-to-point head motion were estimated for each subject (Murphy *et al.*, 2007; Van Dijk *et al.*, 2012). Excessive head motion (cumulative motion translation or rotation $>3 \, mm$ or $3°$ and mean point-to-point translation or rotation $>0.15 \, mm$ or $0.1°$) was applied as an exclusion criterion. Point-to-point motion was defined as the absolute displacement of each brain volume compared with its previous volume. None of the participants had to be excluded. Two-sample *t*-tests yielded no significant differences between groups regarding mean point-to-point translation or rotation of any direction ($P > 0.10$) as well as temporal signal-to-noise ratio ($P > 0.50$). Further control for head motion effects was carried out in the network construction procedure.

Topological analysis of whole brain functional connectivity network

Network construction

For each subject, the whole brain functional connectivity network was constructed from preprocessed resting-state functional MRI data. We defined 112 nodes by anatomical parcellation of the whole brain using Harvard-Oxford atlas (Supplementary Table 1; FSL, Oxford University). Time series of functional MRI signal were extracted from each voxel and subsequently averaged within each region of interest. The regional time courses were then regressed against confounding covariates (comprising six time courses of head motion and signals derived from whole grey matter, white matter and CSF). Maximal overlap discrete wavelet transform was applied to decompose the residual regional time series into the following four frequency scales: scale 1 (0.125–0.250 Hz), scale 2 (0.060–0.125 Hz), scale 3 (0.030–0.060 Hz) and scale 4 (0.015–0.030 Hz) (Percival and Walden, 2000). Absolute wavelet correlation coefficients at the low-frequency scale 2 (0.060–0.125 Hz) were used for further analysis according to previous studies (Lynall *et al.*, 2010; Alexander-Bloch *et al.*, 2012). Finally, a 112×112 connectivity matrix representing individual whole brain functional connectivity network was obtained for each subject.

Network analysis

To prepare graph-based topological analysis of the functional connectivity network, binary networks were generated for the cost range from 0.05–0.50 (with intervals of 0.01) using Prim's algorithm of minimum spanning tree in-line with previous work (Alexander-Bloch *et al.*, 2012). The cost of a network is defined as the number of existing edges divided by the number of all possible edges and serves as a basic 'economical' constraint on brain networks (Bullmore and Sporns, 2012). Cost range 0.05–0.5 was selected because networks with cost <0.05 are too sparse to obtain stable network topology and those with cost >0.50 become increasingly random and lose their small-world property that is characteristic for human brains (Humphries *et al.*, 2006; Lynall *et al.*, 2010). In addition, to investigate the impact of costs on network topology, four arbitrary quasi-equidistant cost sub-ranges (i.e. 0.05–0.14, 0.15–0.24, 0.25–0.34 and 0.35–0.50) were defined.

Graph analysis of binary networks was carried out in Matlab using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010). Global topological properties of characteristic path length, global efficiency, and global betweenness-centrality (all reflecting functional integration;

Rubinov and Sporns, 2010), and clustering coefficient and small-worldness (reflecting functional segregation and its relation to functional integration; Rubinov and Sporns, 2010) were calculated (Supplementary Methods) and averaged across costs for each subject. Group comparison was carried out for each cost sub-range by permutation test (100 000 iterations; $P < 0.05$) controlling for age, gender and total grey matter volume (Supplementary Methods, grey matter volume was provided by structural voxel-based morphometry analysis). Correspondingly, to analyse the topology of nodal connectivity, nodal efficiency and centrality (represented by nodal degree and betweenness-centrality; Rubinov and Sporns, 2010) were calculated and compared across groups (permutation test, 100 000 iterations, $P < 0.05$). One should note that, although efficiency, degree and betweenness-centrality reflect different aspects of functional integration, they are not completely independent among each other (i.e. they correlate significantly for specific nodes (Valente *et al.*, 2008; Lynall *et al.*, 2010; Bassett *et al.*, 2012; Zuo *et al.*, 2012). Nodal analysis was restricted to scores of centrality and efficiency within the low cost sub-range (0.05–0.14) due to results of global property analysis. After previous studies, false positive correction for *N*-node statistical comparison was applied using 1 / (amount of nodes) = 1 / 112 = 0.009 as significance threshold (Lynall *et al.*, 2010).

Partial correlation analysis for topology scores, number of depressive episodes and current symptoms

To analyse the relationship of both the course of major depression and current depressive symptoms with topological properties of nodal connectivity independently of each other, we calculated the partial correlation coefficients between topological scores and both the number of depressive episodes and HAM-D scores in patients ($P < 0.009$, false positive correction); partial correlation analysis was controlled for several variables including particularly structural changes, medication and disease duration (see below). Partial correlation analysis was used because it allows for measuring the degree of association between two random variables (i.e. topological score and number of episodes), with the effect of controlling variables removed (e.g. current symptoms reflected by HAM-D). In more detail, the partial correlation between a given topological score and the number of depressive episodes given controlling variables Z = (HAM-D, age, gender, grey matter volume, duration, medication), written as ρ(Top score, Number of depressive episodes;·Z), is the correlation between the residuals R(Top score) and R(Number of depressive episodes) resulting from the linear regression of Top score with Z and of Number of depressive episodes with Z, respectively. Therefore, a partial correlation-based approach enables the analysis of the relationship between a topological property and the course of major depression while controlling for the effect of current symptoms and vice versa.

To control for potential confounding effects, we included age, gender, grey matter volume, medication, accumulated stress, and disease duration as covariates-of-no-interest into our partial correlation approach. First, the functional connectivity of intrinsic brain networks depends on widespread structural integrity of polysynaptic pathways (Lu *et al.*, 2011). As we focus on changes of functional integration among the whole brain network that are independent of structural changes (MacQueen *et al.*, 2003; Frodl *et al.*, 2008; Kronmuller *et al.*, 2009), we included total grey matter volume scores as covariate-of-no-interest in the above mentioned functional connectivity analyses to control for this influence of structural variations (for structural changes in patients see voxel-based morphometry analysis in the Supplementary Methods). Second, patients of our study were treated by antidepressant medication, which has been demonstrated to affect intrinsic functional connectivity (Delaveau *et al.*, 2011). Therefore,

control for medication effects is necessary. Different from antipsychotic drugs, which can be compared by chlorpromazine equivalents, no comparable approach exists currently for antidepressants. We developed two ways to control for antidepressant effects and evaluated them among each other and with previous findings: (i) we divided applied antidepressants and augmentation medication into four classes (selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor, noradrenergic and specific serotonergic antidepressants, and atypical antipsychotics); then we defined a medication covariate by the number of different classes a patient received in the partial correlation analysis; (ii) in a validation analysis, we defined four covariates (i.e. one for each medication class) with numbers 1 or 0: 1 means the patient was treated by this medication class whereas 0 means they were not. Third, as we were interested in the relationship between nodal connectivity topology and number of episodes independent of disease duration and accumulated stress, we included disease duration and the number of episodes triggered by stressful life events as additional covariates. Thereby we assume that the number of such stress-triggered episodes reflects patient's accumulated stress relevant for depression course.

Results

Global and regional atrophy in patients

Patients' total grey matter volume was reduced; regional brain volume reduction was found in the anterior cingulate cortex, dorsal prefrontal cortex, and hippocampus amongst other areas (Supplementary Fig. 2 and Supplementary Table 2). This result is in line with previous findings (Savitz and Drevets, 2009).

Aberrant global functional integration in patients

For the first cost-sub-range from 0.05 to 0.14, all subjects had small-worldness scores >1.22, demonstrating for all subjects brain networks with small-world property (Supplementary Table 3). Across groups, small-worldness and global clustering coefficient did not differ significantly (Fig. 1 and Table 2). In patients, global efficiency was reduced, global betweenness-centrality and characteristic path length were increased (Fig. 1 and Table 2). Cost range analysis revealed that changes of global topological scores were mainly driven by the low-cost sub-range (0.05–0.14), i.e. by connections of strong functional connectivity (Fig. 1).

Aberrant nodal efficiency and centrality in patients

Altered nodal centrality and efficiency of node-centred connectivity was found for several regions in patients (Fig. 2 and Table 3). In the striatum, patients had increased nodal betweenness-centrality in the right putamen and decreased nodal degree and efficiency in the caudate. In the frontal cortex, patients had decreased nodal degree in the inferior frontal gyrus pars triangularis and decreased nodal efficiency in the orbital gyrus. Furthermore, patients had increased nodal degree in the occipito-temporal cortex and decreased nodal betweenness-centrality in the postcentral gyrus.

Depressive symptoms were associated with the nodal connectivity topology of areas known to be part of the salience and default mode networks
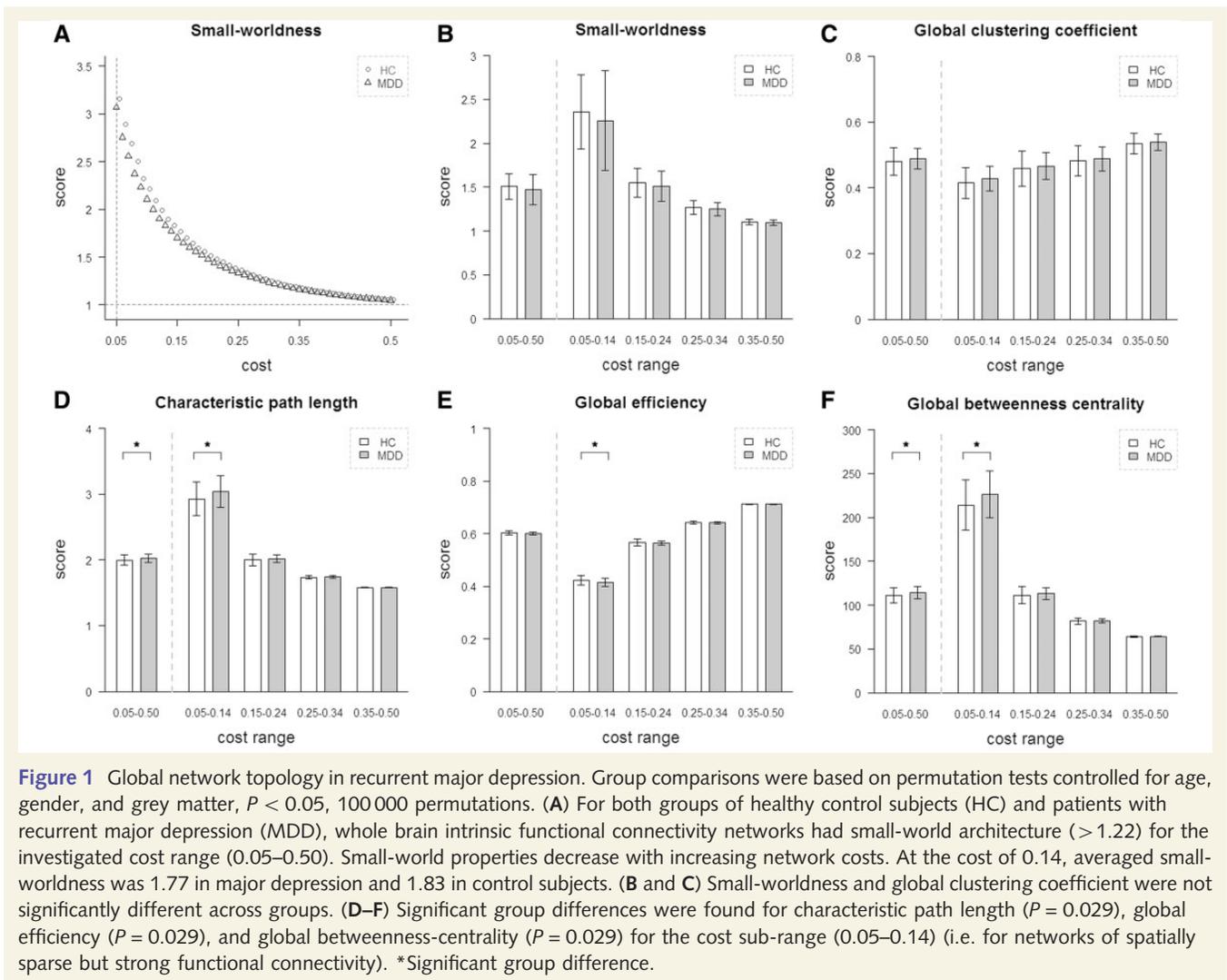
To investigate the relationship among connectivity topology, disease course and depressive symptoms, we applied partial correlation analysis of corresponding scores with additional covariates of age, gender, grey matter volume, medication, accumulated stress and disease duration. To control for medication effects, we used two different ways to model medication influences; as results of both models differed only marginally, we report only results of the first model in which the number of medication classes administered to the patient constituted the medication covariate. To facilitate comprehensive evaluation of partial correlation results, we first examined the relationship among covariates by Pearson's correlation: HAM-D and the number of depressive episodes were not correlated (r = 0.041, P = 0.844); number of depressive episodes was correlated with disease duration (r = 0.784, P < 0.001), and HAM-D with the number of medication classes administered to the patient (r = 0.569, P = 0.003). No further covariate showed significant correlation with number of depressive episodes or HAM-D (P > 0.05). Additionally, total grey matter volume was significantly correlated with age (r = −0.649, P = 0.0004) and disease duration was also correlated with age (r = 0.459, P = 0.021). For partial correlation results regarding connectivity topology, critically, we found that patients' HAM-D scores were negatively correlated with nodal degree of the inferior frontal gyrus and positively correlated with nodal betweenness-centrality of the posterior supramarginal gyrus (Table 4). The inferior frontal gyrus is a hub of the salience network, and the posterior supramarginal gyrus of the default mode network.

The number of depressive episodes is associated with aberrant topology of striatal connectivity independently of current symptoms

In patients' right putamen, the number of depressive episodes was positively correlated with nodal efficiency of connectivity, independently of current symptoms, medication status, disease duration and additional covariates (Fig. 3 and Table 4). In addition, significant association between nodal degree of the nucleus accumbens' connectivity and number of depressive episodes was found (Fig. 3 and Table 4).

Discussion

To analyse how the topology of the brain's intrinsic functional connectivity network is linked with the course of depressive episodes in major depression, we applied resting-state functional MRI and

Figure 1 Global network topology in recurrent major depression. Group comparisons were based on permutation tests controlled for age, gender, and grey matter, $P < 0.05$, 100 000 permutations. (**A**) For both groups of healthy control subjects (HC) and patients with recurrent major depression (MDD), whole brain intrinsic functional connectivity networks had small-world architecture (>1.22) for the investigated cost range (0.05–0.50). Small-world properties decrease with increasing network costs. At the cost of 0.14, averaged small-worldness was 1.77 in major depression and 1.83 in control subjects. (**B** and **C**) Small-worldness and global clustering coefficient were not significantly different across groups. (**D–F**) Significant group differences were found for characteristic path length ($P = 0.029$), global efficiency ($P = 0.029$), and global betweenness-centrality ($P = 0.029$) for the cost sub-range (0.05–0.14) (i.e. for networks of spatially sparse but strong functional connectivity). *Significant group difference.

Table 2 Global topological network properties in recurrent major depression

	Healthy controls	Patients with MDD	P-Value
Small-worldness	2.344 ± 0.407	2.271 ± 0.570	0.300
Global clustering coefficient	0.412 ± 0.044	0.431 ± 0.037	0.055
Characteristic path length	2.923 ± 0.244	3.049 ± 0.215	0.029*
Global efficiency	0.423 ± 0.018	0.414 ± 0.014	0.029*
Global betweenness-centrality	213.492 ± 27.086	227.438 ± 23.841	0.029*

Group comparisons: permutation tests (100 000 permutations); *Significant result for $P < 0.05$; group comparisons were controlled for age, gender, and total grey matter volume. Global network scores are reported as mean and SD for cost sub-range 0.05-0.14. MDD = major depressive disorder.

graph-based network analysis in patients with recurrent depression, and healthy control subjects. We found selective association between aberrant topology of the right putamen's connectivity and patients' number of depressive episodes, independently of current depressive symptoms, medication status, accumulated stress and disease duration. This result provides first evidence that intrinsic functional network organization is linked with the course of major depression, more specifically that the aberrant topology of striatal connectivity is associated with the number of episodes in depression. Data suggest that striatum's connectivity

may interact with the course of depressive episodes, potentially contributing to depressive relapse risk in major depression.

Aberrant topology of striatal connectivity is associated with the course of major depression

Topology of striatal connectivity was found to be associated with the course of depressive episodes in patients with recurrent major

depression (Fig. 3, Tables 3 and 4). Specifically, we found a positive correlation between the number of episodes of major depression and nodal efficiency of right putamen intrinsic connectivity in patients (Fig. 3 and Table 4). Right putamen's centrality was significantly increased in patients (Fig. 2 and Table 3), i.e. the stronger the putamen's hubness, the more depressive episodes. Both efficiency and centrality (the latter comprising degree and betweenness-centrality) reflect functional integration in the brain
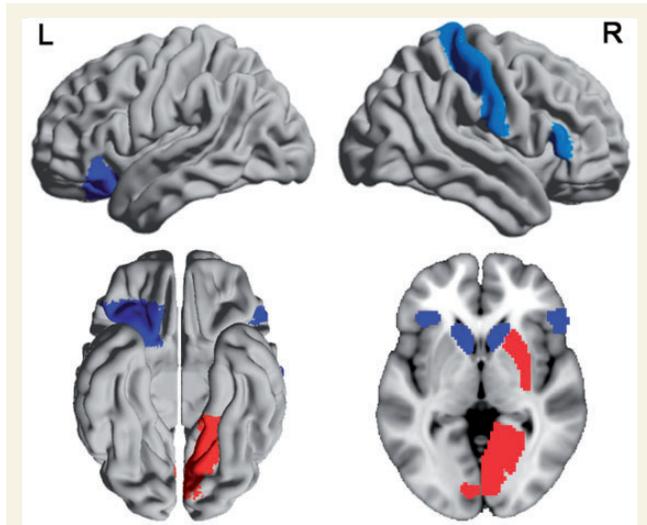
Figure 2 Brain regions with aberrant nodal efficiency and centrality in recurrent major depression. Group comparisons were based on permutation tests controlled for age, gender and grey matter volume, $P < 0.009$ based on false positive correction for multiple testing, 100 000 permutations. Coloured regions indicate significantly changed nodal intrinsic functional connectivity network topology (i.e. nodal efficiency or centrality) in patients. Blue/red indicates decrease/increase of a topological property in patients. For more details see Table 3. L = left; R = right. This figure was visualized with the BrainNet Viewer (http://www.nitrc.org/projects/bnv/).

i.e. the ability to rapidly combine information from distributed brain regions (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). Furthermore, we found correspondent results for the ventral striatum (Fig. 3 and Table 4) (i.e. we found a positive correlation between nucleus accumbens' centrality and the number of depressive episodes), suggesting that the topology of whole striatum's connectivity is associated with the course of episodes in major depression. Findings were not explained by age, gender, medication effects or total grey matter changes, for which we controlled statistically. Findings were also controlled for total disease duration and number of episodes triggered by stressful life events, suggesting that specifically the number of episodes and not disease duration or accumulated stress is linked with the topology of striatal connectivity. Importantly, results were also controlled for the degree of current symptoms, indicating that the topology of striatal connectivity reflects major depression's course rather than its symptoms.

Between-group differences of nodal network topology included bilateral caudate and right putamen (Fig. 2 and Table 3). Putamen's intrinsic functional connectivity pattern is preferentially linked with the insula and anterior cingulate cortex, i.e. with key regions of the salience network, whereas the caudate's connectivity links more with areas of the default mode network (such as the medial prefrontal and posterior cingulate cortex) (Di Martino et al., 2008). Both salience and default mode networks are strongly involved in major depression (Greicius et al., 2007; Sheline et al., 2010; Hamilton et al., 2011; for review Whitfield-Gabrieli and Ford, 2012; Hamilton et al., 2013). A previous study reported increased putamen and caudate centrality/efficiency in first-episode major depression patients (Zhang et al., 2011). Concerning putamen we found consistent results in patients with recurrent major depression, and concerning caudate we found reduced centrality and efficiency in patients with recurrent major depression. It might be that within the dorsal striatum, network topology of sub-areas (like putamen and caudate) develops distinctively in the course of recurrent major depression potentially because of a specific intrinsic connectivity pattern (see further

**Table 3 Nodal network topology in recurrent major depression**

Lobe	Node / Region of interest	Side	Mode	Healthy controls	Patients with MDD	P-Value
Patients with MDD > Healthy controls						
Subcortical	Putamen	R	BC	175.898 ± 126.037	346.133 ± 230.110	<0.001
Occipital	Intracalcarine cortex	R	Deg	7.672 ± 4.071	11.031 ± 4.838	0.006
		L	Deg	7.615 ± 4.095	12.446 ± 5.376	<0.001
	Lingual gyrus	R	Deg	8.649 ± 4.593	12.801 ± 6.334	0.005
Patients with MDD < Healthy controls						
Subcortical	Caudate	R	E_{nodal}	0.390 ± 0.071	0.319 ± 0.088	0.002
		L	Deg	9.162 ± 5.632	5.071 ± 4.237	0.002
			E_{nodal}	0.402 ± 0.074	0.325 ± 0.081	0.001
Frontal	Frontal orbital cortex	L	E_{nodal}	0.462 ± 0.048	0.417 ± 0.059	0.003
	Inferior frontal gyrus, pars triangularis	R	Deg	10.010 ± 5.859	6.158 ± 3.543	0.003
Sensorimotor	Postcentral gyrus	R	BC	234.044 ± 154.870	138.132 ± 78.231	0.004

Group comparisons: permutation tests (100 000 permutations); reported results are significant for $P < 0.009$ based on false positive correction for multiple testing; group comparisons were controlled for age, gender and total grey matter volume. Nodal network scores are reported for cost sub-range 0.05-0.14 as mean and SD. MDD = major depressive disorder; R = right; L = left; BC = nodal betweenness-centrality; Deg = nodal degree; E_{nodal} = nodal efficiency.

Table 4 Nodal network topology: partial correlation with depressive symptoms (HAM-D) and major depression course (number of depressive episodes), respectively

Lobe	Node / Region of interest	Side	Mode	r-Value	P-value
Association between nodal network topology and depressive symptoms					
Frontal	Inferior frontal gyrus, pars triangularis	R	Deg	−0.614	0.005
Parietal	Supramarginal gyrus, posterior division	R	BC	0.688	0.001
Association between nodal network topology and number of depressive episodes					
Subcortical	Putamen	R	E_{nodal}	0.588	0.008
	Accumbens	R	Deg	0.586	0.008

Partial correlation analyses were corrected for age, gender, total grey matter volume, disease duration, and medication effects; reported results are significant for $P < 0.009$ based on false positive correction for multiple comparison. Regional network scores are based on cost sub-range 0.05–0.14. R = right; L = left; Deg = nodal degree; E_{nodal} = nodal efficiency; BC = nodal betweenness-centrality.
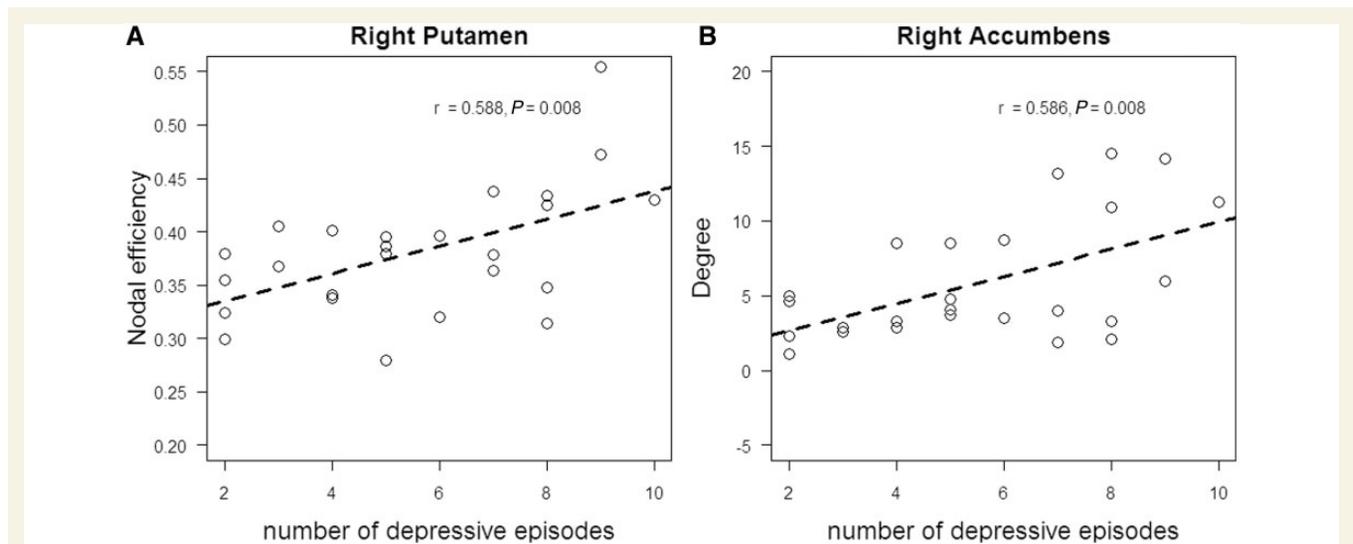
Figure 3 Association between striatal connectivity topology and number of depressive episodes in patients with recurrent major depression, independently of current symptoms and disease duration. Partial correlation analysis of nodal topological scores and number of depressive episodes, including additional covariates of current symptoms, age, gender, grey matter brain volume, medication effects and disease duration, $P < 0.009$ based on false positive correction for multiple testing. Scatter plots reflect significant correlations between different striatal network scores and the number of depressive episodes in patients with recurrent major depression.

support for this argument below). However, we cannot exclude the potential influence of methodological differences between the previous and our study [e.g. Zhang *et al.* (2011) applied a brain atlas different from that of our study; such atlas-based parcellation change may shift the network topology result; Wang *et al.* (2009)]. Future studies, which should be designed to study explicitly data of both first and recurrent episode major depression, are necessary to compare directly network topology changes within one methodological framework.

Two lines of research highlight the importance of the striatum (particularly of the right putamen) for major depression: (i) Impaired emotion processing in major depression: a recent meta-analysis in major depression, which integrated PET-based metabolic resting-state findings with functional MRI data of emotional stimulation, found that patients' aberrant striatal activity might prevent critically the regulatory impact of the prefrontal cortex on increased emotional processing in limbic-insular areas

(Hamilton *et al.*, 2012). The authors suggest that changes of striatal connectivity (particularly of the dorsal striatum) may contribute to this regulatory deficit, potentially because of lowered striatal dopamine levels (Hamilton *et al.*, 2012). Our result is consistent with this idea, highlighting explicitly the important role of increasingly changed topology of striatal connectivity for the course of major depression; and (ii) Impaired emotional learning in major depression: furthermore, dopamine-dependent striatal activity is essential for reinforcement learning (Liljeholm and O'Doherty, 2012). This type of learning is impaired in major depression (Eshel and Roiser, 2010). For example, during reversal learning, right putamen responses for unexpected reward were selectively reduced in patients with major depression (Robinson *et al.*, 2012). The authors suggest that a reward-related dysfunction of the right putamen within a striatum-centred prefrontal-limbic circuit may inhibit the learning of appreciating and enjoying positive life experience; such positive experience, in turn, is critical for depressive

recovery. Our result is consistent with this idea, specifying that right putamen's connectivity topology might be relevant for such adaptive processes in major depression. In summary, aberrant topology of striatal connectivity and its link with the course of depressive episodes are consistent with models of impaired emotion regulation and dopamine-dependent reward learning in major depression.

Aberrant topology of striatal connectivity and depressive relapse risk

Aberrant topology of striatal connectivity might be a potential mechanism to mediate the relapse risk in major depression. Depressive episodes are associated with both the change of network topology (Figs 1 and 2) and the increase of episode relapse risk (Hardeveld *et al.*, 2010). Here we found that the amount of episodes is specifically linked with aberrant topology of striatal connectivity (Fig. 3). This link suggests striatal topology as neural correlate for the course of episodes in major depression, and therefore of episode relapse. This argument makes topology of striatal connectivity a potential biomarker to evaluate depressive recurrence risk.

Aberrant nodal network topology in areas of the salience network is associated with current depressive symptoms

Beyond the striatum, aberrant nodal centrality and efficiency was found in the inferior frontal gyrus, the orbitofrontal cortex as well as in the occipital and somatosensory cortex (Fig. 2 and Table 3). This finding was not influenced by age, gender, medication status, or total grey matter reduction. With respect to affected regions, our result matches perfectly previous findings in first-episode major depression (Zhang *et al.*, 2011); as mentioned above for the caudate, the direction of changes was different for some regions (e.g. patients' lingual or calcarine centrality was reduced in the previous but increased in our study). Nodal degree and efficiency of inferior frontal gyrus' and posterior supramarginal gyrus' connectivity, respectively, was specifically associated with depressive symptoms measured by the HAM-D (Table 4). These areas are key regions of the salience and default mode network, which both are critically involved in depressive symptoms such as rumination or aberrant emotional reactivity (Greicius *et al.*, 2007; Sheline *et al.*, 2010; Hamilton *et al.*, 2011, 2013; Whitfield-Gabrieli and Ford, 2012). Aberrant network topology and the association of network topology with depressive symptom severity overlapped in the inferior frontal gyrus of the salience network (Tables 3 and 4). This result suggests that topological changes of the cortical salience network reflect major depression symptoms, whereas those of the subcortical striatum are associated with the course of major depression. This finding is in line with the more general idea about cortex-basal-ganglia (including striatum)-thalamus-cortex loops, where the cortex itself initially generates action/cognition/affective candidates, between which the basal ganglia then arbitrate (likely based on their learned

reinforcement probabilities) to facilitate (gate) the 'best' one (for review see Maia and Frank, 2011).

Aberrant global network topology in recurrent major depression: impact on the backbone network

Concerning global topology of functional connectivity, we found selectively aberrant functional integration (decreased global efficiency and increased global betweenness-centrality) in patients, whereas other topological properties (small-worldness and clustering coefficient) were not significantly different across groups (Fig. 1 and Table 2). In general, global topological scores are derived from correspondent nodal scores by different forms of averaging. Because of the correspondence of decreased global efficiency/decreased caudate efficiency and increased global betweenness-centrality/increased putamen betweenness-centrality, selective reorganization of global functional integration seems to depend mainly on the reorganization of striatal connectivity in major depression, emphasizing the prominent role of striatal connectivity in recurrent major depression.

Furthermore, changes of global network topology are driven by low-cost networks i.e. by networks that include edges of particularly strong intrinsic functional connectivity. Across investigated cost-sub-ranges, significant group differences of network topology focus on the cost-sub-range of 0.05–0.14, which is related to sparse networks and strong connectivity (Fig. 1). This means that recurrent major depression is selectively associated with changes in widespread (whole brain) strong (top 14%) functional connections, which are supposed to constitute the backbone of the brain network. Previous studies found that backbone networks consist mainly of both network hubs and strong long-distance edges (Serrano *et al.*, 2009; van den Heuvel *et al.*, 2012; Markov *et al.*, 2013). Correspondingly, we found global and nodal centrality, which are both related to such hubness, to be altered in patients. Taken together, these data indicate that major depression is particularly associated with changes in the brain's backbone network.

Methodological issues and limitations

To evaluate results of the current study appropriately, some methodological issues have to be considered. Issues concerning patient sample and chosen graph approach are discussed below and, issues concerning study design and imaging data analysis are discussed in the Supplementary Discussion.

Medication

Patients in our study were treated by antidepressant medication. Although recent studies suggest that antidepressants normalize brain function (Anand *et al.*, 2005; Fu *et al.*, 2007; Heller *et al.*, 2013), the impact of antidepressants on intrinsic functional connectivity is so far incompletely understood (Bruhl *et al.*, 2010; Delaveau *et al.*, 2011). To control for potential impact of medication, we modelled medication effects and added corresponding covariates into statistical analyses. As no canonical way to account

for antidepressants effects is available, we tested two different models, which yielded almost identical results. Further, we found that medication status was associated with the degree of current symptoms but not with the number of episodes, suggesting that at least during a current episode the amount of applied antidepressants is independent of the previous disorder course but dependent on symptom severity. In summary, these findings and the coherence of our results with previous studies (Zhang *et al.*, 2011; Wang *et al.*, 2013), suggest that medication may not critically influence results of our study. Nevertheless, data should be interpreted carefully because of potential medication confounds. Future studies in non-medicated patients are necessary; however, such studies in drug-free patients of recurrent major depression might implicate strong practical and ethical problems.

Binary graph approach

In this study, instead of weighted graphs, the binary undirected graph-based framework was used to analyse the brain's intrinsic functional connectivity network. Binary undirected graphs are defined by edges of either 1 or 0 (i.e. they reflect the presence or absence of connections due to a given threshold), whereas weighted graphs reflect connection strengths by continuous edge scores (Rubinov and Sporns, 2010). The binary approach was chosen for the following reasons: (i) Backbone network and weaker connection analysis: in contrast to weighted graph approaches (Rubinov and Sporns, 2011), binary approaches enable a cost analysis (i.e. an edge density analysis) to evaluate separately the brain's backbone network (defined by strongest edges for all nodes) and the influence of weaker connections (i.e. edges of weaker connectivity strength) on network topology. In particular, we found that major depression is associated with changes in the backbone network; (ii) Comparability between binary and weighted graph approaches: cost integration within binary approaches (i.e. averaging of graph metrics across costs) provides results that are comparable with those derived from weighted graph approaches (Ginestet *et al.*, 2011); and (iii) Comparability with other studies: previous studies of brain network topology in major depression relied on binary undirected graphs (Jin *et al.*, 2011; Zhang *et al.*, 2011; Tao *et al.*, 2013). We used the same framework to enable comparisons among studies. Nevertheless, it should be noted that weighted approaches conserve more information about the whole distribution of edge weights than binary approaches do. Future complementary studies using weighted graphs might be helpful to understand more comprehensively brain organization changes in major depression.

Conclusion

In recurrent major depression aberrant topology of striatal connectivity is associated with the course of depressive episodes independently of current symptoms, medication status, accumulated stress, and disease duration. Therefore, the topology of striatum's intrinsic connectivity may have the potential to predict episode relapse risk in major depression.

Supplementary material

Supplementary material is available at *Brain* online.

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