Imbalance in Subregional Connectivity of the Right Temporoparietal Junction in Major Depression

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Abstract: Major depressive disorder (MDD) involves impairment in cognitive and interpersonal functioning. The right temporoparietal junction (RTPJ) is a key brain region subserving cognitive-attentional and social processes. Yet, findings on the involvement of the RTPJ in the pathophysiology of MDD have so far been controversial. Recent connectivity-based parcellation data revealed a topo-functional dualism within the RTPJ, linking its anterior and posterior part (aRTPJ/pRTPJ) to antagonistic brain networks for attentional and social processing, respectively. Comparing functional resting-state connectivity of the aRTPJ and pRTPJ in 72 MDD patients and 76 well-matched healthy controls,

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we found a seed (aRTPJ/pRTPJ) × diagnosis (MDD/controls) interaction in functional connectivity for eight regions. Employing meta-data from a large-scale neuroimaging database, functional characterization of these regions exhibiting differentially altered connectivity with the aRTPJ/pRTPJ revealed associations with cognitive (dorsolateral prefrontal cortex, parahippocampus) and behavioral (posterior medial frontal cortex) control, visuospatial processing (dorsal visual cortex), reward (subgenual anterior cingulate cortex, medial orbitofrontal cortex, posterior cingulate cortex), as well as memory retrieval and social cognition (precuneus). These findings suggest that an imbalance in connectivity of subregions, rather than disturbed connectivity of the RTPJ as a whole, characterizes the connectional disruption of the RTPJ in MDD. This imbalance may account for key symptoms of MDD in cognitive, emotional, and social domains. *Hum Brain Mapp 00:000–000, 2016*.

Key words: major depressive disorder; depression; right temporoparietal junction; resting state; connectivity; functional magnetic resonance imaging

INTRODUCTION

Mental disorders considerably contribute to the global health challenge, with depressive disorders being the leading global cause of all non-fatal burden of disease [Whiteford et al., 2013]. Major depressive disorder (MDD) involves impairment in various domains, including cognitive and interpersonal social functioning [Hammar and Ardal, 2009; Wells et al., 1989]. Cognitive impairment is not generally attributable to psychotropic medication and comprises deficits in attention and executive function as well as visuospatial learning and memory [Porter et al., 2003]. Furthermore, there is evidence for abnormalities in all domains of higher social cognition, similarly independent from psychiatric medication and notably also from the aforementioned neurocognitive deficits [Doose-Grünefeld et al., 2015; Ladegaard et al., 2014]. The advent of neuroimaging techniques has provided insight into the neural mechanisms underlying these disturbances on the emotional and behavioral level [Cusi et al., 2012; Disner et al., 2011]. Due to its physiological implication in both cognitive-attentional and social processing [Bzdok et al., 2013; Krall et al., 2015], the right temporoparietal junction (RTPJ) is an interesting candidate region for dysfunction of both domains. A recent quantitative meta-analysis of functional imaging studies did reveal disturbed neural activity of the RTPJ in MDD patients [Diener et al., 2012], but other studies have not provided evidence in this regard [Fitzgerald et al., 2008; Hamilton et al., 2012; Kühn and Gallinat, 2013; Sacher et al., 2012]. This discrepancy is surprising and might be explained by the heterogeneity of experimental paradigms that are pooled in a given meta-analysis. If a brain region comprises highly specialized subregions with differential connectivity profiles, the meta-analytic integration of various experiments may produce a null result for the region as a whole.

The RTPJ is a supramodal association area that significantly contributes to both specific cognitive attentional and specific social processes. A recent connectivity-based parcellation study, however, revealed a topofunctional dualism within the RTPJ, by demonstrating that the anterior and posterior part of this region are linked to antagonistic brain networks for attentional and social processing, respectively [Bzdok et al., 2013]. More specifically, the anterior RTPJ increases neural activity concomitantly with a midcingulate–motor–insular attention network and decreases neural activity when a parietal network crucial for social cognition and memory retrieval becomes active. The reverse pattern was found for the posterior RTPJ [Bzdok et al., 2013]. Given that these mental processes are affected in individuals suffering from MDD [Ladegaard et al., 2014; Porter et al., 2003], we hypothesized that an imbalance in the connectivity of these RTPJ subregions is part of the MDD pathophysiology.

To test this hypothesis, we investigated whether MDD is associated with a differential disruption of connectivity of the anterior and posterior RTPJ (aRTPJ/pRTPJ) subregions, possibly accounting for pertinent psychopathology. A two-step approach was used. First, we compared functional resting-state connectivity of the aRTPJ and pRTPJ in patients suffering from MDD and healthy controls recruited from two sites. In addition, we assessed correlations of dysconnectivity with both the clinical course of MDD and current depressive symptoms. Second, regions that demonstrated differentially altered connectivity with the aRTPJ/pRTPJ were then functionally characterized using meta-data from a large-scale neuroimaging database.

METHODS

Subjects

Seventy-two patients with the diagnosis of MDD according to ICD-10 and 76 healthy controls without any current or past neurological or psychiatric disorders from two different sites (Göttingen [Site 1; $N = 100$] and Munich [Site 2; $N = 48$]) participated in this study. All subjects provided written informed consent in accordance with the guidelines of the local ethics committees at the Universities in Göttingen and Munich. Patients and controls were matched not only at the overall group level but also within

TABLE I. Participants' characteristics

	Site 1			Site 2			All participants		
	Patients	Controls	*P* value	Patients	Controls	*P* value	Patients	Controls	*P* value
Subjects [*N*]	49	51		23	25		72	76	
Age [yr]	34.00 ± 10.55	34.04 ± 10.92	0.986	47.87 ± 15.14	44.08 ± 14.78	0.385	38.43 ± 13.73	37.34 ± 13.11	0.623
Gender [M/F]	22/27	22/29	0.859	12/11	14/11	0.790	34/38	36/40	0.986
Age of onset[a]	27.79 ± 11.38	N/A	N/A	31.74 ± 13.57	N/A	N/A	29.54 ± 12.43	N/A	N/A
Duration[a] **[yr]**	9.28 ± 10.11	N/A	N/A	16.13 ± 9.85	N/A	N/A	12.31 ± 10.48	N/A	N/A
Episodes[b] **[*N*]**	4.84 ± 3.90	N/A	N/A	5.26 ± 2.32	N/A	N/A	5.04 ± 3.22	N/A	N/A
BDI-II[b]	21.92 ± 9.78	N/A	N/A	23.65 ± 6.05	N/A	N/A	22.75 ± 8.17	N/A	N/A

[a]Data available for 29 patients at Site 1 and all 23 patients at Site 2 (i.e., for 52 patients in total).
[b]Data available for 25 patients at Site 1 and all 23 patients at Site 2 (i.e., for 48 patients in total).
Values are reported as mean ± standard deviation. *P* values were determined by a two-sample t test for age and a χ^2 test for gender.
BDI-II, Beck Depression Inventory-II [Beck et al., 1996]; N/A, not applicable.

each site with respect to age, gender, and within-scanner movement (Table I and Supporting Information Table 1). The portion of patients with recurrent episodes of depression was 67%, while 33% experienced their first episode at the time of study participation. In eight patients, the major depressive episode was accompanied by psychotic symptoms. Twenty-one patients had psychiatric comorbidities, reflecting the common and prevalent comorbidity spectrum of MDD [Kessler et al., 2003]: ten anxiety disorders, eight personality disorders (including borderline, obsessive-compulsive, and dependent subcategories), one attention deficit hyperactivity disorder, one dysthymia, one posttraumatic stress disorder, and one somatoform disorder. Patients with bipolar disorder, schizoaffective disorder, schizophrenia, and substance dependence were excluded from this study. Two patients were free of any psychotropic medication. Forty-one patients received antidepressant mono-therapy, 19 patients dual-therapy, and 10 patients triple-therapy, involving a total of 17 different compounds (Supporting Information Table 2). All healthy control subjects were free of any psychotropic medication.

Imaging Data Acquisition

MRI was performed at 3T MR scanners (TrioTim, Siemens/Achieva, Philips; Site 1/Site 2) with similar protocols. For coregistration with the functional scans and volumetric analysis, structural data were provided by a three-dimensional, T_1-weighted, magnetization-prepared rapid gradient-echo sequence (MP-RAGE; echo time = 3.26/4.00 ms; repetition time = 2,250/9 ms; flip angle = 9/8°; voxel size = 1 × 1 × 1/1 × 1 × 1 mm^3). Functional data were obtained using a gradient-echo echo planar imaging sequence (GE-EPI; echo time = 30/35 ms, repetition time = 2,000/2,000 ms, flip angle = 70/82°, matrix = 64 × 64/96 × 96, 33/32 slices, slice thickness = 3/4 mm, 0.6/0 mm interslice gap, voxel size = 3 × 3 × 3/2.3 × 2.3 × 4 mm^3). Subjects were instructed to lie still during the scanning session (6/10 min) and to let their mind wander, but not to fall asleep. Debriefing after scanning indicated that none of the subjects fell asleep during the scanning period.

Preprocessing and Statistical Imaging Data Analysis

Functional connectivity

The first four functional scans were discarded to account for signal saturation. The remaining images were preprocessed using the SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm). Hereby, EPI images were first corrected for movement artifacts by affine registration using a two-pass procedure. Mean EPI images of each subject were then spatially normalized to the Montreal Neurological Institute (MNI) single-subject template [Holmes et al., 1998] using the "unified segmentation" approach [Ashburner and Friston, 2005]. The ensuing deformation parameters were applied to the individual EPI volumes, which were then smoothed by a 5 mm full width at half maximum (FWHM) Gaussian kernel. This relatively small kernel was used to maintain high spatial precision since we investigated adjacent subregions of the RTPJ.

The aRTPJ and pRTPJ seed regions were taken from a recent data-driven characterization that revealed a subspecialization in the RTPJ using connectivity-based parcellation (cf., Fig. 1) [Bzdok et al., 2013]. Seed regions are available at the Archive of Neuroimaging Meta-Analyses (ANIMA) [Reid et al., in press]. The time series from each voxel in both seed regions were processed as follows [Satterthwaite et al., 2013]: To reduce the likelihood of spurious correlations, variance possibly explained by three nuisance variables was removed: (1) the six motion parameters derived from the image realignment and their squared versions, (2) the first derivative of the realignment parameters and their squared versions, and (3) mean white matter and cerebrospinal fluid signal time courses. There were no systematic group differences in head motion,

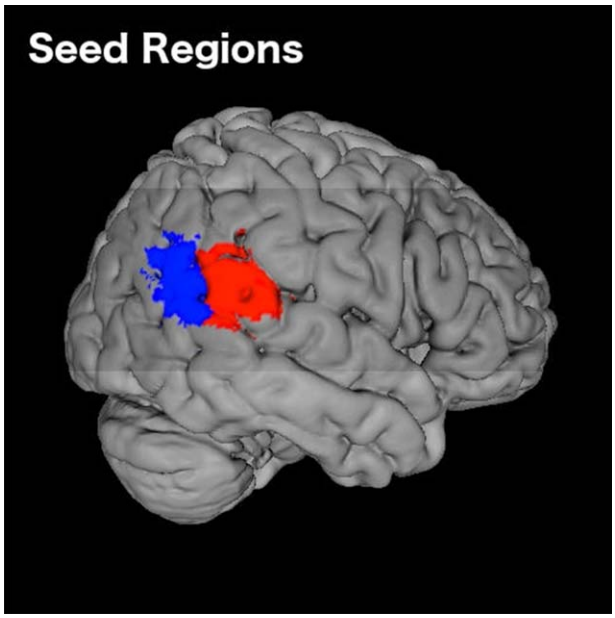

Figure 1.
The aRTPJ (red) und pRTPJ (blue) seed regions were taken from a recent data-driven characterization that revealed a subspecialization in the RTPJ using connectivity-based parcellation [Bzdok et al., 2013].

neither within nor across the samples of both sites (cf., Supporting Information Table 1). This is noteworthy, since head motion can introduce spurious signal correlations [Power et al., 2015]. Group matching with respect to motion parameters is necessary to exclude systematic motion artifacts as the source of between-group differences in connectivity, even if neurobiological traits may be linked to differences in motion [Zeng et al., 2014].

Data were then filtered preserving frequencies between 0.01 and 0.08 Hz, given that meaningful resting-state correlations will predominantly be found in this frequency range because the blood oxygen level dependent response acts as a low-pass filter [Biswal et al., 1995; Fox and Raichle, 2007]. The time course of the respective seed was then expressed as the first eigenvariate of its voxels' time courses and compared to time series of all other gray matter voxels in the brain by computing Pearson's correlation coefficients. These coefficients were then transformed into Fisher's z scores and subsequently included in an ANOVA accounting for non-sphericity of the data. Age, sex, and site were included as covariates in the analyses to remove possibly confounding effects. We tested for significant seed (aRTPJ/pRTPJ) $\times$ diagnostic group interactions ($P < 0.05$, familywise error (FWE) corrected on cluster level).

To analyze the relationship between both the clinical course of MDD and current depressive symptoms with dysconnectivity, we assessed correlations of functional connectivity between the seed and the previously located dysconnected regions (i.e., clusters under the significant interaction term) with age of disease onset, disease duration, number of depressive episodes, and Beck's Depression Inventory (BDI-II [Beck et al., 1996]) scores in follow-up analyses. Age, sex, and site were included as covariates in the analyses to remove possibly confounding effects. Results were regarded as significant if they passed $P < 0.05$, FDR corrected. Here, controlling for false discovery rate (FDR) was applied due to compact support, that is, because the dysconnected clusters are discrete objects that are not spatially correlated [Chumbley and Friston, 2009]. That is, whereas we controlled the cluster-level FWE in the whole-brain analysis, we could not use this (spatially-based) method for the follow-up assessment of the ensuing (discrete) regions and hence used FDR (which in turn is invalid for spatially smooth data as in the voxel-wise analysis) correction for multiple comparisons.

Voxel-based morphometry

To scrutinize whether potential dysconnection was based on structural alteration, we compared local gray matter volume of the ensuing and seed regions between both groups using voxel-based morphometry (VBM).

The structural scans were preprocessed using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) with standard settings (DARTEL normalization, spatially adaptive nonlinear means denoising, a Markov random field weighting of 0.15, bias field modeling with a regularization term of 0.0001 and a 60 mm full width at half maximum (FWHM) cutoff). The resulting gray matter segments, modulated for the nonlinear components of the deformations into standard space, were input to the statistical analysis.

Gray matter volume of the candidate regions was compared between MDD patients and controls employing ranksum tests. Age, sex, and site were included as covariates in the analyses to remove possibly confounding effects. To maintain high sensitivity to regional structural alterations, we applied an uncorrected significance threshold of 0.05.

Anatomical allocation

For anatomical labeling, we capitalized on cytoarchitectonic maps of the human brain provided by the SPM8 Anatomy Toolbox [Eickhoff et al., 2005, 2006, 2007]. Clusters were thus assigned to the most probable histologically defined brain area at the respective location.

Functional Characterization

Functional characterization intends to link topographically defined brain regions with corresponding psychological processes by testing which kind of experiments are most likely to activate a given region. To functionally characterize regions with dysconnectivity to RTPJ subregions (i.e., the regions revealed by the interaction analysis), we made use of the BrainMap database (http://www.

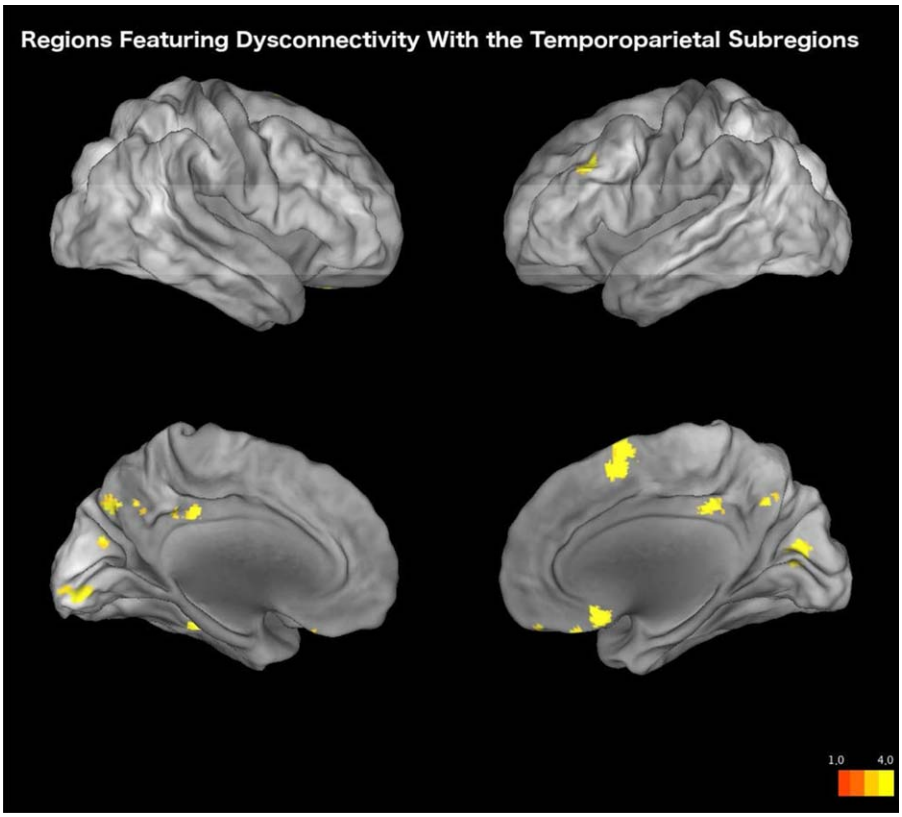

Figure 2.
Significant seed (aRTPJ/pRTPJ) × diagnosis interactions in whole-brain resting state connectivity analyses ($P < 0.05$, cluster-level FWE corrected; cf. Table II). The color bar depicts *z* scores.

brainmap.org) that currently contains ≈ 7,500 experiments in healthy subjects (experiments investigating age, gender, disease, or drug effects excluded). BrainMap meta-data provide information on behavioral domain and paradigm class of each neuroimaging experiment included in the database. Behavioral domains describe the mental processes isolated by the statistical contrasts [Fox et al., 2005] and comprise the main categories action, cognition, emotion, interoception, perception, as well as their subcategories. Paradigm classes specify the task employed in the respective neuroimaging studies (see http://www.brainmap.org/scribe/for the complete BrainMap taxonomy). To describe the functional roles of the dysconnectivity regions, we used a reverse inference approach, which tests the probability of a mental process being present, given knowledge that a particular brain region is activated [Bzdok et al., 2013]. More precisely, a region's functional profile was determined by over-representation of mental processes (i.e., behavioral domains and paradigm classes) in the experiments activating the respective cluster relative to the entire BrainMap database using a binomial test [Bzdok et al., 2013; Reetz et al., 2012]. The significance threshold was set to $P < 0.05$, corrected for multiple comparisons using FDR as for the other follow-up analyses. This approach provides an objective and quantitative attribution of mental functions to brain regions in contrast to commonly used qualitative and subjective interpretation of task-based activation foci in neuroimaging. That is, while acknowledging potentially disparate roles of cortical modules between task- and rest-state, we here examined which kind of tasks are significantly associated with the (resting-state) findings to provide an objective functional characterization of these dysconnected regions.

RESULTS

Brain Imaging Data

Functional connectivity

We observed significant seed (aRTPJ/pRTPJ) × diagnostic group interactions, indicating subregional RTPJ dysconnectivity, with eight regions (cf., Fig. 2 and Table II).

Patients with MDD exhibited an increased (i.e., stronger) positive connectivity with the pRTPJ and at the same time an increased (i.e., stronger) negative connectivity with the aRTPJ with several midline regions, more specifically the precuneus, subgenual anterior cingulate cortex (sgACC)

TABLE II. Brain regions with subregional dysconnectivity to the right temporoparietal junction in major depression

Brain region			MNI coordinates				Connectivity with aRTPJ		Connectivity with pRTPJ	
Macroanatomic	Cytoarchitectonic	Cluster size in voxels	*x*	*y*	*z*	*Z* score	in controls	in patients	in controls	in patients
L/R Precuneus	7P/M	228	−10	−68	40	4.60	0	-	+	**+**
L Parahippocampus		94	−38	−32	−22	4.45	0	-	0	+
sgACC/mOFC		140	4	20	−18	4.38	0	-	-	+
L dlPFC		171	−38	32	32	4.25	**+**	+	0	+
PCC		170	−4	−32	36	4.01	-	**-**	0	+
pMFC	Area 6	285	2	10	62	5.13	+	**+**	+	0
L dVC	Area 17/18	121	−4	−88	−6	4.63	-	0	0	-
R dVC	Area 17/18	172	4	−76	16	4.38	0	+	+	-

Significant seed (aRTPJ/pRTPJ) × diagnosis interactions in whole-brain resting state connectivity analyses ($P < 0.05$, cluster-level FWE corrected). Coordinates represent peaks within a cluster. For detailed information on cytoarchitectonics, see publications by Amunts and colleagues (Area 17/18), Geyer (Area 6), and Scheperjans and colleagues (7M/P) [Amunts et al., 2000; Geyer, 2004; Scheperjans et al., 2008a,b].

aRTPJ, anterior right temporoparietal junction; dlPFC, dorsolateral prefrontal cortex; dVC, dorsal visual cortex; L, left; MNI, Montreal Neurological Institute; mOFC, medial orbitofrontal cortex; PCC, posterior cingulate cortex; pMFC, posterior medial frontal cortex; pRTPJ, posterior right temporoparietal junction; R, right; sgACC, subgenual anterior cingulate cortex.

+/0/-, positive/no/negative connectivity: bold font marks stronger connectivity in case of same direction of connectivity preference in patients and controls.

extending into the medial orbitofrontal cortex (mOFC), and posterior cingulate cortex (PCC). Another midline region, the posterior medial frontal cortex (pMFC), featured a reduction of positive connectivity with the pRTPJ and at the same time an increase of positive connectivity with the aRTPJ, resulting in a reversal of its subregional RTPJ connectivity preferences (cf., Fig. 3 and Table II). Post hoc tests indicated a significant main effect of group for altered functional connectivity of the pRTPJ with precuneus and pMFC, respectively.

Connectivity of the dorsal visual cortex (dVC) with the pRTPJ bilaterally shifted towards negative values. In contrast, its connectivity with the aRTPJ moved towards positive values, yielding a decoupling of the left and a positive coupling of the right dVC. Furthermore, we found a specific reduction of positive aRTPJ connectivity with the left posterior dlPFC along the inferior frontal sulcus. Finally, the left parahippocampus also showed a significant interaction, driven by enhanced positive pRTPJ and enhanced negative aRTPJ connectivity (cf., Fig. 3 and Table II). Post-hoc tests indicated a significant main effect of group for altered functional connectivity between aRTPJ and left dlPFC as well as between pRTPJ and right dVC.

Altered connectivity with RTPJ subregions was correlated with course and current state of the disease in three regions (cf. Fig. 4). Connectivity of the precuneus with the aRTPJ was found to be the stronger (pathologically) negative, the higher the patient's BDI score ($r = -0.30$). Similarly, early onset of disease was linked to stronger negative connectivity between PCC and aRTPJ ($r = 0.37$). Finally, pathological decrease in positive connectivity between pMFC and pRTPJ was associated with higher number of depressive episodes ($r = -0.58$), early onset ($r = 0.42$), and longer duration of disease ($r = -0.33$). In summary, more severe depression was associated with the pathological aRTPJ-precuneus, early onset of disease with the pathological aRTPJ-PCC, and frequent relapses with the pathological pRTPJ-pMFC connectivity shift (cf. bar graphs in Fig. 3).

Voxel-based morphometry

There were no statistically significant differences in gray matter volume of the eight regions featuring dysconnectivity with the a/pRTPJ between MDD patients and controls, even at the employed lenient significance threshold. Similarly, no morphological differences with respect to the aRTPJ and pRTPJ subregions could be observed between groups.

Functional Characterization

To obtain an objective description of the tasks recruiting the regions that were found in the resting-state analysis and hereby provide possible links to the psychopathology of MDD, we conducted a functional characterization of regions with differential subregional RTPJ dysconnectivity. Hereby, psychological terms were related to the respective region as registered in the BrainMap database, i.e., on basis of functional experiments in healthy subjects (cf., Supporting Information Fig. 1).

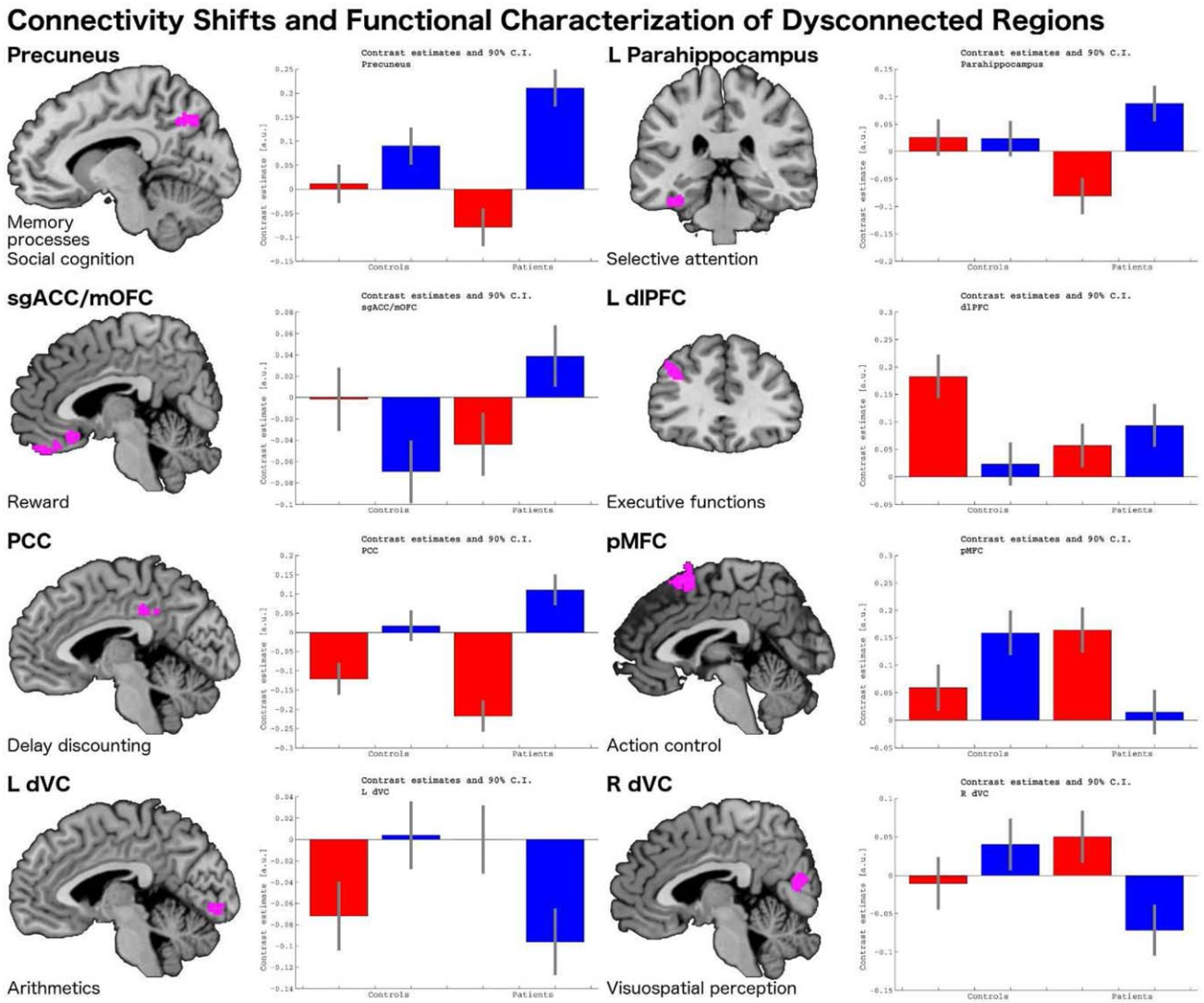

Figure 3.

Overview of opposite shifting in connectivity with aRTPJ/pRTPJ and summary of the functional characterization for each region. Connectivity with aRTPJ/pRTPJ is depicted in red/blue colors. aRTPJ, anterior right temporoparietal junction; a.u., arbitrary units; C.I., confidence interval; dlPFC, dorsolateral prefrontal cortex; dVC, dorsal visual cortex; L, left; MDD, major depressive disorder; mOFC, medial orbitofrontal cortex; PCC, posterior cingulate cortex; pMFC, posterior medial frontal cortex; pRTPJ, posterior right temporoparietal junction; R, right; sgACC, subgenual anterior cingulate cortex.

The dlPFC and parahippocampus were significantly associated with cognitive functions, namely task switching (dlPFC) and monitoring/discrimination tasks (parahippocampus). The pMFC cluster was significantly associated with action execution and inhibition, that is, behavioral control. A significant above-chance association with reward processing and reward control was found for the sgACC/mOFC and PCC clusters, respectively. The dVC clusters in turn were related to tasks requiring visuospatial attention, including counting and mental rotation paradigms. Finally, a significant association with memory processes and social cognition was identified for the precuneus.

Synopsis of Brain Imaging and Functional Characterization

As depicted in Figure 3, functional characterization linked regions featuring subregional RTPJ dysconnectivity to cognitive (dlPFC, parahippocampus) and behavioral

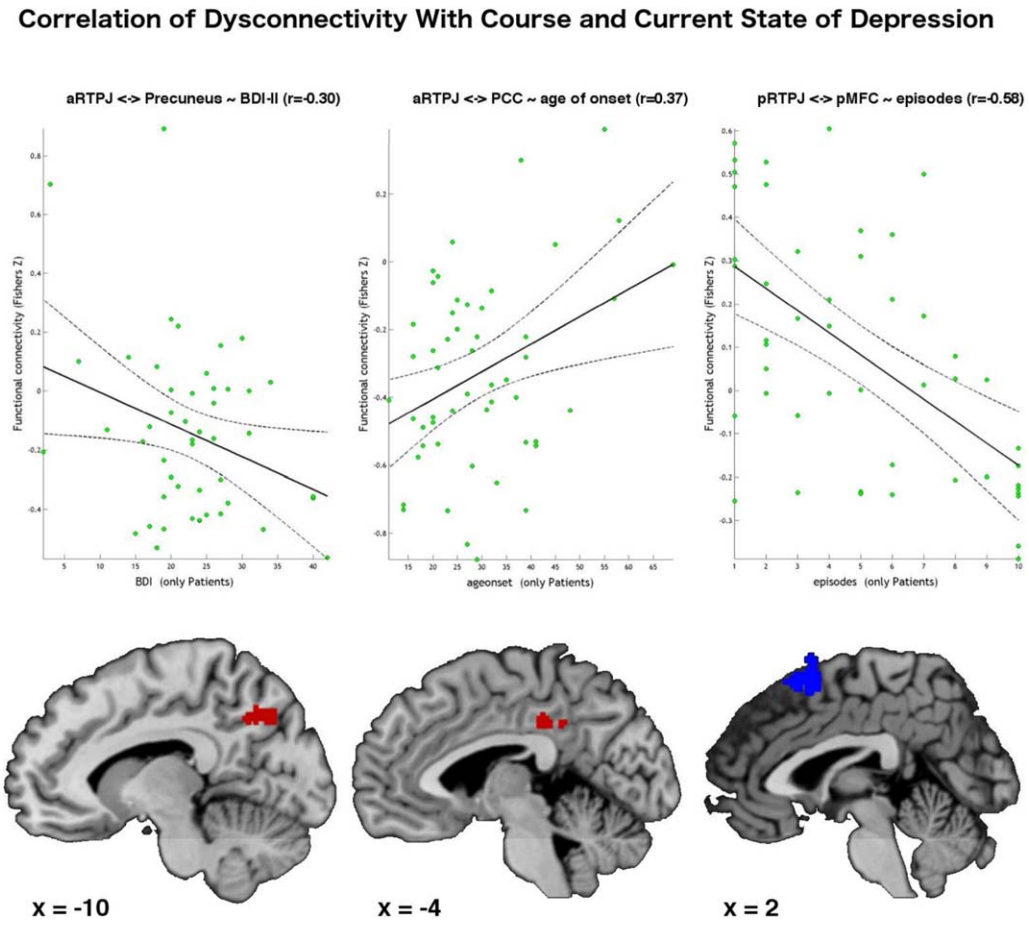

Figure 4.

Scatter plots illustrating significant correlations of altered connectivity between aRTPJ/pRTPJ subregions and PCC, precuneus as well as pMFC with BDI-II scores, age of disease onset, and number of depressive episodes ($P < 0.05$, FDR corrected). Functional connectivity between pRTPJ and pMFC was additionally correlated with age of disease onset ($r = 0.42$) and duration of disease ($r = -0.33$). Brain slices are shown at coordinates (*x*, *y*, *z*) in MNI space. aRTPJ, anterior right temporoparietal junction; BDI-II, Beck's Depression Inventory [Beck et al., 1996]; MNI, Montreal Neurological Institute; PCC, posterior cingulate cortex; pMFC, posterior medial frontal cortex; pRTPJ, posterior right temporoparietal junction.

(pMFC) control, visuospatial processing (dVC), reward (sgACC, mOFC, PCC), as well as memory retrieval and social cognition (precuneus). Regions related to social cognition and reward processing were characterized by a positive hyperconnectivity with the pRTPJ and contrariwise a negative hyperconnectivity with the aRTPJ. Cognitive control regions showed a dissociation of connectivity preferences in the same direction as these regions, that is, increased positive connectivity with pRTPJ and connectivity changes with the aRTPJ toward negative values. For regions associated with behavioral control and visuospatial processing, by contrast, reverse connectivity changes were observed, i.e., a shift in the positive direction for aRTPJ and in the negative direction for pRTPJ.

DISCUSSION

We investigated functional connectivity in patients with MDD; our analyses targeted the RTPJ, which is a key brain region subserving cognitive-attentional and social processes [Bzdok et al., 2013; Krall et al., 2015]. Although it is well-known that these processes are significantly impaired during a depressive episode, findings on the involvement of the RTPJ in the pathophysiology of MDD have so far been controversial [Diener et al., 2012; Fitzgerald et al., 2008; Hamilton et al., 2012; Kühn and Gallinat, 2013; Sacher et al., 2012]. Here, we demonstrated diametrically altered functional connectivity of the anterior and posterior RTPJ, affecting precuneus, PCC, pMFC, sgACC, mOFC, left parahippocampus, and dlPFC, as well as

bilateral dVC. These results suggest that imbalanced connectivity of both previously defined subregions, rather than of the RTPJ as a whole, characterizes the connectional disruption of the RTPJ in MDD. Moreover, a main effect of group was found for only a minority of the functional connections. This indicates that a/pRTPJ are not per se differentially connected in MDD but rather exhibit an imbalance in functional connectivity.

Linking Pathophysiology to Psychopathology

Data-driven functional characterization of the dysconnected regions using the large-scale BrainMap database provided a possible link between such pathophysiology and psychopathology associated with MDD. In that context, it must be noted that we assessed which kind of experiments are more likely than chance to recruit the identified regions of interest in healthy subjects. While we acknowledge that the hereby-identified roles may not correspond directly to processes used in the resting state, this provides the currently most objective functional interpretation of neuroimaging findings. Using this approach, we observed that the functional roles of the respective regions pertained to cognitive and behavioral control as well as visuospatial processing, reward, and social processing. Disturbance of these mental processes on the behavioral level is reflected in the diagnostic criteria of MDD, which include anhedonia, that is, diminished pleasure in most activities, as well as reduced attention and ability to concentrate, causing significant distress or impairment in social functioning.

Neuropsychological studies and their meta-analytic synopses have substantiated specific neurocognitive deficits. In particular, there is strong evidence for impaired attention [Lee et al., 2012; Rock et al., 2014], memory [Lee et al., 2012; McDermott and Ebmeier, 2009; Rock et al., 2014], and executive functions [Henry and Crawford, 2005; Lee et al., 2012; McDermott and Ebmeier, 2009; Rock et al., 2014; Snyder, 2013] in MDD patients. This symptom complex matches very well with our finding of subregional RTPJ dysconnectivity to left parahippocampus as well as dlPFC and with their functional association with attentional and executive processes. Furthermore, it is in line with corresponding dysconnectivity to the left and right dVC that were linked to arithmetic and visuospatial operations implicating memory processes. While the aRTPJ may be considered part of an externally oriented, stimulus-driven attention network, the pRTPJ appears to be part of an internally oriented, stimulus-independent memory-related network [Bzdok et al., 2013]. Given this distinction and their antagonism as outlined above, it is notable that in MDD the "attentional" dlPFC and parahippocampus as well as the "memory-associated" dVC show a connectivity imbalance in favor of their "non-genuine" networks, that is, the former regions a preference for the pRTPJ and the latter a shift towards positive connectivity with the aRTPJ. It has also been shown that cognitive performance, specifically in the domains "memory" and "executive functions", is correlated with current depression severity [Halvorsen et al., 2012; Lee et al., 2012; McDermott and Ebmeier, 2009], even though executive dysfunction may represent more a trait-like marker of MDD [Douglas and Porter, 2009; Lee et al., 2012]. These relationships are in line with the correlation of more severe course of disease (operationalized by age of onset, duration, and number of episodes) with altered functional connectivity to the pMFC, which in turn was associated with executive functions.

Cognitive flexibility, especially in the context of attentional and executive control tasks, is modulated by emotion in patients with MDD [Murphy et al., 2012]. Notably, emotional stimulation is accompanied by hypofunction of the RTPJ in MDD [Moratti et al., 2008]. Both these observations may be neurobiologically based on the imbalance in subregional RTPJ connectivity to regions that are crucial for cognitive control and motivational/reward processing (sgACC, mOFC, PCC, pMFC), as evidenced by our functional connectivity analyses. This seems to apply especially to the PCC, associated with cognitive reward control (delay discounting), that is, an interaction of cognitive and emotional control processes. The correlation of early disease onset with stronger negative connectivity between PCC and aRTPJ as well as its reciprocal relationship with decreased connectivity between pMFC and pRTPJ support previous findings of an association of early-onset depression with a deficit in the approach motivation system [Shankman et al., 2007]. In contrast to connectivity changes of aforementioned regions (parahippocampus, dlPFC, dVC) towards "non-genuine" networks, the specific imbalance of the reward-related sgACC/mOFC and PCC is characterized by a positive hyperconnectivity with their "genuine" pRTPJ and a negative hyperconnectivity with their "non-genuine" aRTPJ networks. This property may imply a certain rigidity of the corresponding networks and consequently—due to the negative hyperconnectivity with the "external" aRTPJ network—a decreased receptivity for external rewards in MDD patients.

In addition, MDD-related neurocognitive deficits seem to be associated with psychosocial dysfunctioning [Evans et al., 2014]. The latter may arise from impaired social decision making [Zhang et al., 2012] or, more generally, from limited social cognition due to patients' difficulties with interpreting cognitive social stimuli [Hörtnagl et al., 2014; Weightman et al., 2014]. These findings are complemented by our demonstration of positive hyperconnectivity between the "social pRTPJ" and the precuneal cluster (which was also associated with social cognition according to the functional characterization analysis) as well as of the latter's concomitant negative hyperconnectivity with the "attentional aRTPJ". That is, similar to that of reward-related regions (sgACC/mOFC, PCC), the precuneal connectional imbalance features an antidromic hyperconnectivity that may manifest itself in sociocognitive rigidity in

MDD. The observed correlation between decreased precuneus-aRTPJ connectivity and BDI-II scores may provide the neurofunctional basis for the known negative association between social cognitive performance and depression severity [Weightman et al., 2014].

Taken together, aberrant subregional functional connectivity of the RTPJ seems to account for common core deficits in MDD patients, more specifically cognitive control, emotional-motivational, and social dysfunction. This diversity of impairment fits well with the notion of the RTPJ as a multimodal association area and can be explained by its subregional network specificity, which is disrupted in MDD patients, as shown in this study. Notably, these connectivity alterations rest upon a concomitant differential alteration in connectivity of the aRTPJ and pRTPJ.

Influence of Medication

It should be noted that the majority of patients received psychopharmacological treatment at the time of assessment. Therefore, doubts may be raised about the specificity of our findings to the disease itself.

Yet, it has to be considered that we are reporting an *interaction* between two temporoparietal subregions and two subject groups. Therefore, *general* effects of medication should not be reflected in the results. Furthermore, medication was very heterogeneous: About 40% ($N = 29$) of the patients were taking multiple compounds and no more than four patients had the same combination of drugs. Furthermore, antidepressant monotherapy ($N = 41$) involved seven different compounds with no more than eight patients taking the same drug. A most recent and comprehensive meta-analysis of antidepressants-related effects on brain activity in depressed patients observed changes in only two regions where we found specifically altered RTPJ dysconnectivity, namely precuneus and left dlPFC [Ma, 2015]. Furthermore, this study proved highly distinct effects of different drug classes, for example, differentially altered activity in ACC, dlPFC, and parahippocampus following selective serotonin and serotonin norepinephrine reuptake inhibitors. In contrast, there is meta-analytic evidence of MDD-related altered activity in all regions featuring dysconnectivity with RTPJ subregions, although not all meta-analyses exclusively involved drug-free subjects [Diener et al., 2012; Fitzgerald et al., 2008; Hamilton et al., 2012; Kühn and Gallinat, 2013; Sacher et al., 2012]. Moreover, the observed changes in connectivity were not global but highly specific to subregions in the RTPJ.

Although we acknowledge concomitant medication as a limitation, there is in summary little evidence suggesting our findings can be attributed to medication effects, given the high diversity of compounds (cf., Supporting Information Table 2); it is notable that our findings emerged despite rather than due to high variability in administered drugs.

Relationship between Functional Dysonnectivity and Morphology

The VBM analysis did not detect any volumetric differences between MDD patients and healthy controls in the candidate regions. This null result is in line with previous coordinate-based meta-analyses of gray matter changes in MDD, which determine minimal convergence across the literature [Bora et al., 2012; Du et al., 2012; Lai, 2013]. From the results of these meta-analyses, only one area possibly overlapped with regions of our findings in the pMFC at a lenient significance threshold [Bora et al., 2012; Du et al., 2012; Lai, 2013]. Hence, aberrant subregional connectivity of the RTPJ in MDD is unlikely to be predicated on morphological brain alterations but likely represents a functional endophenotype for MDD.

Practical Relevance

The results of this study are novel and may be regarded as important from a theoretical point of view. Nevertheless, practical implications and applicability must not be disregarded. A straightforward and generally well-tolerated approach for modulating neural activity in distinct brain areas is noninvasive brain stimulation. Randomized and doubleblind trials employing repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) targeting mostly the dlPFC showed, in comparison with sham-stimulation, significant and clinically relevant antidepressant effects that are comparable with those of commercially available antidepressant drugs [Berlim et al., 2013, 2014; Kalu et al., 2012; Shiozawa et al., 2014]. Accordingly, it has been proposed that future studies should move away from establishing the efficacy of current stimulation protocols against placebo treatment and focus instead on improving the therapeutic effects by for instance targeting alternative brain regions [Berlim et al., 2014]. Given its central and superficial location, the RTPJ seems to be an ideal target region for non-invasive brain stimulation. In fact, rTMS over the RTPJ has been shown to attenuate distress caused by tinnitus [Plewnia et al., 2007], a condition that is commonly linked to depression [Langguth et al., 2011]. Furthermore, a case study reported a resolution of psychotic depression following a right temporoparietal lesion [Chimowitz and Furlan, 1990]. Given its multimodal connectivity profile, as indicated by our functional characterization analysis, neuromodulation of the RTPJ may tackle a diversity of depressive symptoms, including cognitive impairment, anhedonia, and altered social cognition.

Conclusion

In summary, this study addresses ambiguous relevance of the RTPJ for the pathophysiology of MDD to date by revealing a highly specific imbalance in connectivity of

subregions that control antagonistic neural networks. Further functional characterization of the dysconnected regions suggested that this imbalance accounts for key symptoms of MDD in the cognitive, emotional, and social domains, linking pathophysiology to psychopathology. Hence, the RTPJ might represent a promising target region for new interventional approaches.

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