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ARTICLE

Severity of current depression and remission status are associated with structural connectome alterations in major depressive disorder

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Abstract

Major depressive disorder (MDD) is associated to affected brain wiring. Little is known whether these changes are stable over time and hence might represent a biological predisposition, or whether these are state markers of current disease severity and recovery after a depressive episode. Human white matter network ("connectome") analysis via network science is a suitable tool to investigate the association between affected brain connectivity and MDD. This study examines structural connectome topology in 464 MDD patients (mean age: 36.6 years) and 432 healthy controls (35.6 years). MDD patients were stratified categorially by current disease status (acute vs. partial remission vs. full remission) based on DSM-IV criteria. Current symptom severity was assessed continuously via the Hamilton Depression Rating Scale (HAMD). Connectome matrices were created via a combination of T1-weighted magnetic resonance imaging (MRI) and tractography methods based on diffusion-weighted imaging. Global tract-based metrics were not found to show significant differences between disease status groups, suggesting conserved global brain connectivity in MDD. In contrast, reduced global fractional anisotropy (FA) was observed specifically in acute depressed patients compared to fully remitted patients and healthy controls. Within the MDD patients, FA in a subnetwork including frontal, temporal, insular, and parietal nodes was negatively associated with HAMD, an effect remaining when correcting for lifetime disease severity. Therefore, our findings provide new evidence of MDD to be associated with structural, yet dynamic, state-dependent connectome alterations, which covary with current disease severity and remission status after a depressive episode.

Introduction

Major depressive disorder (MDD) is associated with widespread brain network dysfunction. "Disconnection syndrome", a term originally coined for schizophrenia [1, 2], has become an emerging concept in MDD [3].

Investigating anatomical connectivity in patients via neuroimaging methods relies on techniques such as diffusion

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magnetic resonance imaging (dMRI). White matter fiber tracts can be analyzed based on their microstructural properties, which can be of use to infer on the integrity of these tracts [4]. Furthermore, network analysis of human brain connectivity has emerged as an effective tool to analyze the human brain's anatomical network organization [5]. Here, gray matter T1-weighted magnetic resonance imaging (MRI) was used to define nodes and dMRI-based tractography to define the connections—or edges—between the nodes creating a structural connectome [6]. Based on the resulting connectivity matrix, graph theory allows for the investigation of global metrics like connectivity strength, shortest path length, efficiency and small-worldedness [7, 8].

Previous graph theory-based connectome analyses in MDD patients employed a variety of analysis strategies and revealed various results: Most studies could not detect differences in global metrices between MDD and HC [9–13]. However, some found reduced structural connectivity in diverse subnetworks [12, 14, 15]. Investigations of white matter microstructure in voxel-based dMRI studies revealed that fractional anisotropy (FA), a dMRI-based marker of white matter structural integrity, is reduced in several white matter tracts in MDD patients [16]. However, it remains unclear whether these alterations reflect current disease severity or rather a stable risk factor in MDD patients as no studies included remitted patients. A meta-analysis suggested reduced fiber integrity in MDD patients with higher illness duration and higher current disease severity without being able to disentangle these factors [17]. Recently, a first longitudinal study suggested possible recovery effects of white matter integrity 2 years after a depressive episode in MDD patients [18].

To summarize, while some studies employed connectome-based analysis strategies on MRI data in MDD patients in recent years, sample sizes are mostly small (all $n < 100$ patients) and studies comprising patients in differing disease stages are lacking, raising the question of state vs. trait alterations of the detected connectome aberrations. This study investigates (1) whether alterations in global network organization is preserved in patients in a well-powered sample (2) whether instead current disease state is associated with measures of connectome analysis in MDD patients (3) whether changes relate more to lifetime disease severity or the current level of depressive symptoms. We hypothesize that while global network organization is not particularly affected in MDD, reduced FA in MDD may be indicative of depressed state and current disease severity.

Methods and materials

Participants

Subjects were part of the Marburg-Münster Affective Disorders Cohort Study (MACS) [19] and were recruited at two sites (Marburg & Muenster, Germany; see ref. [20] for the quality assurance protocol and [19] for a general description). In total, $n = 920$ participants were available (Marburg: 295 MDD, 270 HC; Münster: 181 MDD, 174 HC). Participants were recruited through newspaper advertisements and local psychiatric hospitals. All experiments were performed in accordance with the ethical guidelines and regulations and all participants gave written informed consent prior to examination. To confirm the psychiatric diagnosis or a lack thereof, the Structural Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) (SCID-I; [21]) was used. MDD subjects were included with current *acute depressive episodes* (MDD-AD) and *partial* (MDD-PR) or *full remission* (MDD-FR) from depression and furthermore, patients could be undergoing in-patient, out-patient, or no current treatment at all. Remission status was determined based on DSM-IV criteria (For more information on this see Supplementary Material 1). Neither the groups (HC vs. MDD) nor the MDD subgroups (MDD-AD, MDD-PR, MDD-FR) differed in composition regarding age and sex (see Table 1). Participants ranging in age from 18 to 65 years were recruited. For exclusion criteria please see Supplementary Material 2. For information on patients' comorbidities and medication see Supplementary Material 3.

MRI data acquisition

In the MACS Study, two MR scanners were used for data acquisition located at the Departments of Psychiatry at the University of Marburg and the University of Münster with different hardware and software configurations (for MRI data acquisition details see Supplementary Material 4). For further details regarding MRI parameters at each site please see our previous work [20]. Therefore, site was included as a co-variate in all models. For more details on the site co-variate, scanner-related investigations, co-variate analyses, and visualization of connectome reconstructions are provided in Supplementary Material 5.

Anatomical connectome reconstruction

Connectome reconstruction involved the following steps [8]. For each subject an anatomical brain network was reconstructed, consisting of 114 areas of a subdivision of the FreeSurfer's Desikan–Killiany atlas [22, 23], and the reconstructed streamlines between these areas. White matter connections were reconstructed using deterministic streamline tractography, based on the Fiber Assignment by Continuous Tracking (FACT) algorithm [24]. We chose for the a basic Diffusion Tensor Imaging (DTI) reconstruction in our case–control study rather than more advanced diffusion direction reconstruction methods to provide a

Table 1 Sociodemographic and connectome data

Characteristic	MDD-AD[a] ($n = 227$)	MDD-PR[a] ($n = 127$)	MDD-FR[a] ($n = 110$)	HC[a] ($n = 432$)	p (all groups)
Sociodemographic					
Gender	♀143♂84	♀83♂44	♀74♂36	♀268♂164	0.733[b]
Age, years	36.53 ± 13.44	36.71 ± 13.45	36.56 ± 13.21	35.58 ± 12.99	0.385[c]
Verbal IQ_{MWTB}	111.68 ± 14.31	113.05 ± 13.65	114.77 ± 13.86	114.51 ± 13.88	0.546[c]
Questionnaires					
HAMD	14.93 ± 6.75	7.88 ± 6.08	2.96 ± 3.30	1.54 ± 2.20	<0.0001[c]
Clinical					
Depressive episodes	4.75 ± 6.21	4.64 ± 5.80	3.37 ± 7.117	–	0.631[c]
Age of onset	25.70 ± 12.50	25.85 ± 12.26	23.45 ± 10.26	–	0.029[c]
Medication					
Medication load	1.72 ± 1.53	1.29 ± 1.25	0.51 ± 0.97	–	0.004[c]
CPZ	36.90 ± 114.93	13.24 ± 47.44	4.76 ± 25.31	–	0.043[c]
Global measures					
PE	736 ± 65	740 ± 65	737 ± 55	737 ± 62	0.920[c]
GE	0.884 ± 0.013	0.885 ± 0.013	0.884 ± 0.012	0.883 ± 0.012	0.834[c]
C	3.600 ± .423	3.593 ± .402	3.609 ± .376	3.624 ± .390	0.915[c]
SW	2.987 ± .306	2.983 ± 0.294	2.989 ± 0.271	3.001 ± 0.285	0.899[c]
S	63725 ± 13762	64268 ± 14724	64848 ± 12888	64709 ± 13448	0.589[c]
NOS	850.82 ± 120.62	850.99 ± 13.50	87.42 ± 12.26	87.19 ± 12.72	0.376[c]
SD	0.0204 ± 0.0031	0.0206 ± 0.0034	0.0202 ± 0.0027	0.0201 ± 0.0029	0.745[c]
FA	0.378 ± 0.017	0.378 ± 0.015	0.382 ± 0.017	0.381 ± 0.016	0.028[c]
Hub measures					
NOS of RC connections	114.796 ± 30.940	120.131 ± 37.398	115.967 ± 31.132	118.888 ± 33.533	0.320[c]
NOS of feeder connections	76.780 ± 13.395	76.352 ± 13.118	78.266 ± 12.796	77.460 ± 12.819	0.834[c]
NOS of local connections	87.920 ± 14.230	87.796 ± 14.735	89.709 ± 14.183	89.393 ± 14.353	0.266[c]
SD of RC connections	0.0271 ± 0.0085	0.0287 ± 0.0102	0.0267 ± 0.0080	0.0272 ± 0.0086	0.442[c]
SD of feeder connections	0.0182 ± 0.0031	0.0183 ± 0.0032	0.0181 ± 0.0029	0.0178 ± 0.0028	0.388[c]
SD of local connections	0.0209 ± 0.0034	0.0210 ± 0.0034	0.0207 ± 0.0029	0.0207 ± 0.0034	0.976[c]
FA of RC connections	0.436 ± 0.025	0.434 ± 0.024	0.439 ± 0.025	0.440 ± 0.024	0.078[c]
FA of feeder connections	0.407 ± 0.017	0.410 ± 0.017	0.411 ± 0.020	0.411 ± 0.018	0.067[c]
FA of local connections	0.352 ± 0.018	0.351 ± 0.017	0.356 ± 0.017	0.355 ± 0.017	0.027[c]

MDD-AD group with current depressive episodes, *MDD-PR* group with partial remission from depression, *MDD-FR* group with full remission from depression, *HC* healthy control group, *HAMD* Hamilton sum score based on 21 items, *CPZ* chlorpromazine equivalent doses, *PE* present edges (based on a binary graph), *L* normalized shortest path length, *GE* normalized global efficiency, *C* normalized clustering coefficient, *SW* Small-worldness, *S* strength (total number of streamlines (i.e., sum of all streamlines)), *NOS* average number of streamlines per present edge, *SD* average streamline density per present edge, *FA* average fractional anisotropy per present edge, *RC* Rich-Club

[a]Numbers present either absolute numbers or mean plus standard deviation

[b]χ^2-test (two-tailed)

[c]F-test (two-tailed)

reasonable balance between false-negative and false-positive fiber reconstructions [25]. We verified our results using higher and lower resolution parcellation of the cortex [23] (Supplementary Material 6). Network connections were included when two nodes (i.e., brain regions) were connected by at least three tractography streamlines [26]. For comparable results in analyses with different thresholds (none, 10) of tractography streamlines see Supplementary Material 6. For each participant, the network information was stored in a structural connectivity matrix, with rows and columns reflecting cortical brain regions, and matrix entries representing the weights of the graph edges. Network edges were weighted according to fractional anisotropy (FA), number of streamlines (NOS), and streamline density (SD) computed as the number of streamlines between two regions divided by their average volume.

Anatomical connectome topology

The topological organization of the anatomical brain networks was assessed using a selection of graph metrics [27]. As an unweighted network edge description we used the total number of present edges (PE), based on a binarized (connection present vs. connection not present) connectivity matrix. Global efficiency (GE) was defined as the average inverse shortest path length between all node pairs, commonly interpreted as a metric of overall communication capacity. Clustering coefficient (C) was computed as the average likelihood that the neighbors of a node are also mutually connected, as a measure of operational segregation. GE and C were normalized in order to account for different numbers of present edges and only normalized measures were used in the analysis. To this end, 1000 random networks were generated from each subject's connectome matrix and the normalized measures were computed as the ratio of the measure and the average measure of the random networks. The Small-world index (SW) was defined as the ratio of the normalized clustering coefficient and the normalized shortest path length. To compare edge weights globally between different groups, for each subject the weights (e.g., global FA, NOS, SD) were averaged over all edges being present in that subject. Overall connectivity strength (S) was computed as the total sum of the number of streamlines of all connections in the network of a given subject.

Rich-Club (RC) organization of complex networks expresses the tendency of high-degree nodes (the degree of a node is the number of connections of this node) to be more strongly interconnected than is to be expected based on their high-degree alone [28]. RC regions—i.e., brain hubs—were defined for each subject individually as the top 15% high-degree nodes (see Supplementary Material 7 for repeated analyses with different thresholds and a different hub definition). Based on the categorization of network nodes into RC (i.e., hub) and non-RC nodes, network edges were classified into three categories: RC connections (edges connecting hub nodes), feeder connections (edges connecting hub to non-hub nodes), and local connections (edges connecting non-hub nodes). RC, feeder, and local weighted connectivity was computed as the sum of the weights of each edge class.

Quality control

Quality control led to the exclusion of two MDD and three HC in the Marburg sample and to the exclusion of three MDD in the Muenster sample (Details shown in Supplementary Material 8). This resulted in a final sample of 291 MDD patients (145 MDD-AD, 91 MDD-PR, and 55 MDD-FR) and 262 HC in Marburg and 173 MDD patients (82 MDD-AD, 36 MDD-PR, 55 MDD-FR) and 170 HC in Muenster (total $n = 896$).

Statistical analysis

Group differences based on remission status

An analysis of covariance (ANCOVA) was used to examine group differences in metrics of brain network topology, accounting for effects of age, sex and site. In total, group status (four groups based on remission status: MDD-AD, MDD-PR, MDD-FR, HC), sex and scanner-site entered into the model as fixed effects terms and age as a co-variate.

Clinical correlates

To check whether possible group differences between MDD subgroups (based on the categorical approach of remission status) are related to current disease severity, we employed a second approach with current depression severity scores as a continuous variable. To this end, connectome metrics showing significant group effects were further examined for an association with current depression severity scores in the MDD subsample. Acute depression severity was measured based on the Hamilton Depression Rating Scale (HAMD) [29]. An ANCOVA was performed with global FA as the dependent variable, sex, site as fixed term effects and HAMD and age as covariates.

We repeated this analysis by separately including further clinical variables that might potentially be related to the HAMD-FA association into the above mentioned ANCOVA model:

(1) Number of depressive episodes; (2) Age of onset; (3) DSM-IV diagnosis of dysthymia; (4) Medication Load Index. For assessing the medication load, we computed an established Medication Load Index [30–32], a composite measure of total medication load reflecting dose and number of prescriptions irrespective of active components. We further examined (5) Level of childhood maltreatment measured with the Childhood Trauma Questionnaire (CTQ, for more information see Supplementary Material 9) and (6) Polygenetic Risk Score (PRS) for Major Depressive Disorder based on a recent Genome-wide association study (GWAS) analysis (see Supplementary Material 9).

Network-based-statistics

To further explore which brain connections are related to the global FA reduction associated with an increased HAMD score within the MDD subsample, we used network-based statistics (NBS) [33] to detect the set of connections related to HAMD. NBS identifies an effect at cluster level by performing mass univariate testing at the edge level controlled for family-wise error (FWE). First, each edge was assigned a t-value obtained from a negative association between FA value und HAMD score while

correcting for age, sex and scanner-site. The test statistic computed for each pairwise association was thresholded to select all supra-threshold links. Next, the largest component of supra-threshold connections was selected to detect the strongest set of HAMD-related connections. Permutation testing (randomizing HAMD scores) using 5000 permutations was performed to ascribe a p-value controlled for FWE to the cluster of HAMD-related edges based on component size. For this analysis, we report and illustrate the component size of significant results based on different t-thresholds in Supplementary Material 10. To illustrate the most affected edges we report on a cluster with a supra-threshold t-value of $t = 2.0$ [33]. Further analyses with more lenient t-thresholds and a larger cluster size are presented in Supplementary Material 11.

Results

Comparison of groups dependent on remission status

Acute depressed, partially remitted, fully remitted MDD patients (MDD-AD, MDD-PR, MDD-FR) and HC did not differ regarding age ($p = 0.726$) and sex ($p = 0.734$). For details see Table 1. MDD subgroups differed in clinical characteristics, with a lower age of onset, higher Medication Load Index and higher prevalence of dysthymia in the MDD-AD group compared to the MDD-FR group (Table 1). Other comorbidities were comparable across MDD subgroups (see Supplementary Material 3).

We found no evidence that groups differed regarding PE ($p = 0.920$), GE ($p = 0.834$), C ($p = 0.915$), SW ($p = 0.899$), S ($p = 0.589$), NOS ($p = 0.376$), and SD ($p = 0.745$). We observed a main effect of group ($F(3889) = 3.124$, $p = 0.025$, $\eta^2 = 0.010$) for FA (see Table 1 for details). Post-hoc t-test revealed reduced FA in MDD-AD compared to MDD-FR ($p = 0.015$, $\eta^2 = .021$) and HC ($p = 0.034$, $\eta^2 = 0.007$). The same pattern was found for MDD-PR, who showed reduced FA compared to MDD-FR ($p = 0.028$, $\eta^2 = 0.018$). See Fig. 1 for details. Results remained consistent across different connectome preprocessing strategies (i.e., for different node parcellations and different minimum number of streamlines please, see Supplementary Material 6 for further details, and for different hub definitions, see Supplementary Material 7).

NOS and SD did not differ across groups in Rich-Club, Feeder or Local connections (all $p > 0.26$). Regarding FA, there was no effect of group in rich club ($p = 0.078$) and feeder connections ($p = 0.067$). The class of local connections showed a main effect of group ($F(3888) = 3.186$ $p = 0.023$). Post-hoc t-tests revealed significantly higher FA in local connections MDD-FR patients compared to MDD-PR ($p = 0.010$) and to MDD-AD ($p = 0.014$).

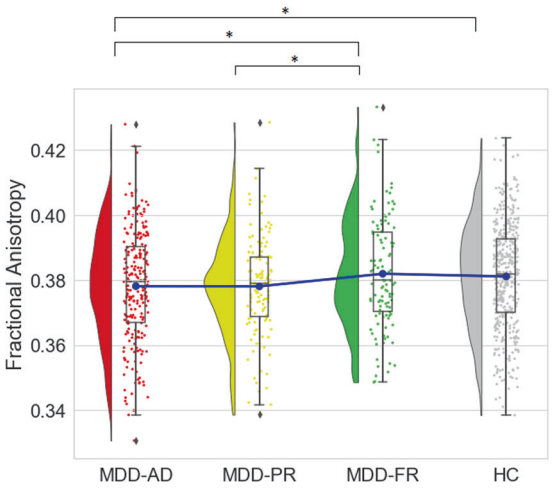

Fig. 1 Raincloud plot [51] of global fractional anisotropy (FA) values. FA values were the mean of all edges. A main effect of group was detected in an ANCOVA correcting for age, sex, and site. Asterisk represents statistical significance ($p < 0.05$) in post-hoc-t-tests. Values are reported for all subgroups: Acute depressed, partially remitted, fully remitted MDD patients (MDD-AD, MDD-PR, MDD-FR; based on DSM-V criteria) and healthy controls (HC). The boxplots display respective sample median alongside interquartile range. The mean value within each group is displayed as a blue dot

Association with current depression severity

Based on the finding of reduced global FA in MDD-AD and MDD-PR we then tested whether FA values were associated with current depression severity (by means of HAMD score) in MDD patients. Analysis revealed a negative association of global FA with HAMD ($F(1457) = 9.337$, $p = 0.002$, $\eta^2 = 0.020$) in an ANCOVA correcting for age, sex, and site. For a scatterplot depicting the HAMD-FA relationship color-coded by remission status please see Supplementary Material 12. Subanalyses analyzing rich club/feeder/local connections revealed no further association of rich club FA with HAMD ($p = 0.208$). FA of feeder connections was significantly negatively associated with HAMD ($F(1457) = 9.016$, $p = .003$, $\eta^2 = 0.019$). FA of local connections also showed a significant negative association with HAMD ($F(1457) = 8.513$, $p = 0.004$, $\eta^2 = 0.018$). For analysis of normality, heterogeneity and corresponding non-linear models see Supplementary Material 13; for power analysis see Supplementary Material 14.

Additional analyses correcting for clinical covariates, childhood maltreatment and genetic risk

ANCOVA analyses revealed a stable global FA—HAMD association even when additionally correcting for number of

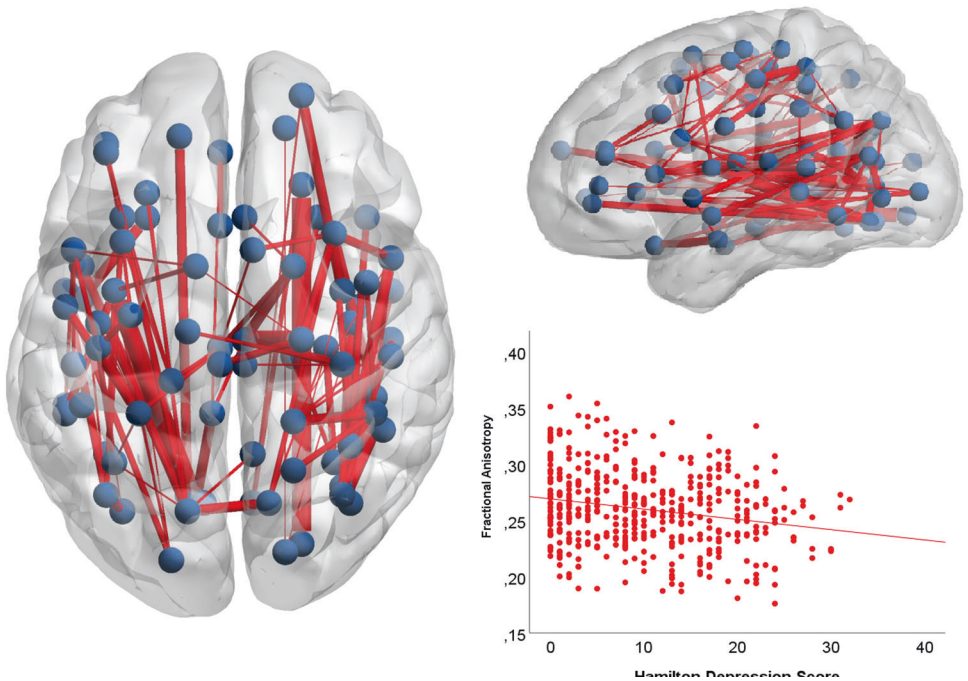

Fig. 2 Edges (red) and nodes (blue) that show a negative association of current depression severity (Hamilton Depression Score) and fractional anisotropy (FA) within the major depressive disorder patient sample. Results show a subnetwork based on a network-based-statistics analysis with a p-value (FWE-corrected) of $p < 0.001$ and a supra-threshold t-value of $t = 2.0$. Images were created using the BrainNet Viewer software [52]. **a** axial view. **b** sagittal view. **c** Scatterplot depicting the association of mean FA (extracted from the significant cluster) and Hamilton Depression Score

depressive episodes (HAMD: $F(1416) = 1.568$, $p = 0.013$, $\eta^2 = 0.015$); diagnosis of dysthymia (HAMD: $F(1456) = 9.095$, $p = 0.003$, $\eta^2 = 0.020$) and Medication Load Index (HAMD: $F(1456) = 5.453$, $p = 0.003$, $\eta^2 = 0.020$; for additional medication analyses see Supplementary Material 15). Correcting for age of onset similarly revealed a stable global FA—HAMD association ($F(1457) = 9{,}337$, $p = 0.002$, $\eta^2 = .020$). Moreover, adding childhood maltreatment (HAMD: $F(1442) = 5.165$, $p = 0.024$, $\eta^2 = 0.012$) or polygenetic risk for depression (HAMD: $F(1206) = 4931$, $p = 0.027$, $\eta^2 = 0.023$) to the model did not alter the observed pattern of results.

NBS analysis

NBS analysis showed a negative association of FA and HAMD in a subnetwork consisting of 94 edges (see Fig. 2 and Supplementary Material 10) at a corrected significance level of $p_{(FWE)} < 0.001$ (NBS t-threshold 2.0). This subnetwork comprised a widespread network, including (orbito-) frontal, temporal, cingulate, parietal, and insular nodes (regions listed in Supplementary Material 10, see also Supplementary Material 11 for additional analysis with a more lenient t-threshold).

Discussion

This study investigated the association of depression status on white matter structure in a sample of depressed and remitted MDD patients. This study contributes to the important question of whether observed connectome alterations are rather a trait or state correlate of MDD. We show that while the general edge topology seems unaffected in MDD patients, effects are observed in connectivity strength (FA) per se, especially depending on current disease severity.

We did not detect any group differences regarding global network features. This finding is in line with several previous studies with smaller sample sizes showing no differences in global metrics like number of present edges, connectivity strength, global efficiency or small-worldness [9, 10]. Also, comparable to the finding of unimpaired global network properties based on streamlines and present edges, no aberrations in subnetworks are found based on hub organization. [30, 34].

Instead, our findings show that MDD is associated with more centralized affected integrity of white matter microstructure of fronto-temporal tracts, and in particular in acute depression. Our results show significantly lower FA in acute depressed vs. fully remitted MDD patients. Additional ANCOVA with a continuous depression score further revealed a negative relationship of HAMD scores and global FA in all patients. NBS analysis further showed that this negative association of HAMD with FA may potentially be mostly driven by a subnetwork including among others orbitofrontal, insular parietal and temporal connections (Fig. 2). This network comprises brain nodes generally implicated in MDD pathophysiology [35] and future studies should investigate whether reduced FA in this network in acute depression serves as an anatomical substrate for known

functional connectivity impairments in MDD within these regions [36].

Disentangling possible influences of current depression severity and lifetime disease severity (age of onset, number of depressive episodes, medication) remains challenging. Further controlling for potential covariates such as age of onset, medication, dysthymia, childhood maltreatment or the polygenetic risk for depression in the ANCOVA did not change the pattern of our findings, supporting the concept of a robust association of acute depression severity with white matter microstructure. Fully remitted patients showed significantly better white matter microstructure than acute depressed patients and with no specific difference to healthy controls. Although care is needed due to the cross-sectional design of the study, numerical FA values in fully remitted MDD patients suggest a level of recovery compared to non-remitted patients.

Our study is cross-sectional in nature, but our findings are in line with the few longitudinal DTI studies in MDD that reported signs of recovery of white matter microstructure disturbances [37]. Furthermore, they are in support of potential slowing of the rate of white matter degradation during the disease course [38]. While underlying cellular mechanisms remain to be understood, evidence suggests that stress-related and immunological changes might mediate the association of depression state and white matter microstructure integrity in MDD [39–42].

The question of whether these observed changes are specific to MDD or whether they reflect overlapping themes of white matter alterations, similar to changes observed in other psychiatric disorders needs to be investigated in direct cross-diagnostic studies. Comparing previous work in schizophrenia (SZ) [7, 43] and bipolar disorder (BP) [44] with our results do suggest differences in connectome aberrations. While SZ patients have been suggested to show reduction of white matter connectivity and global changes in network topology [45], we could not detect strong effects in global network organization in our MDD patients, which suggests a relative preserved general connectome topology in MDD. FA analysis on rich-club, feeder and local connections further revealed similar levels of impairment in MDD, with no specific emphasis on hub connectivity [46]. Future large-scale structural connectome studies focusing on the remission status of psychiatric disorders in relationship to white matter organization [47] are of general interest.

Several methodological points have to be taken into consideration when interpreting the findings of this study. FA as a marker of white matter microstructure is related to many different types of tissue change (e.g., membrane permeability, crossing of fibers), which makes interpretation about the neurobiological meaning of DTI metrics challenging [48]. However, FA has proven useful in the past as a marker of pathological effects in MDD [16, 30] and has shown relevance in its positive association to several cognitive domains [49]. Second, statements about remission and recovery need to be treated with caution, as this study is cross-sectional. However, there are no differences in most demographic and clinical characteristics in the MDD subgroups. Adding characteristics that did display significant differences between the MDD subgroups (medication, dysthymia, etc.), into the regression models did not alter the observed results. Moreover, as current disease severity and remission status are related, disentangling separate effects of those two concepts within a cross-sectional study is challenging. Future longitudinal studies are needed to further support the observed effects of both remission status and current disease severity on FA. Third, addressing the influence of medication, especially lifetime medication load, on brain structure is challenging in a cross-sectional design. However, analyses with current medication load did not reveal any specific association with white matter microstructure in this sample. Fourth, it is important to mention that the observed effects of FA were small, making it unlikely for structural connectome investigations in the future to uncover a sole neurobiological substrate for the multidimensional etiology of the relapsing-remitting pattern of MDD. Although small in effect size (comparable to other genetic and brain imaging studies in psychiatric disorders [50]), our results do present important new evidence for a possible dynamic role of white matter structural connectivity in MDD remission. Finally, we cannot exclude the possibility of having missed even smaller effects in the other global metrics (GE, C, SW, etc.). However, power analyses revealed sufficient power to detect relevant effects for global connectome metrics.

Our findings show that connectome alterations, specifically impairment of white matter microstructure in a large subnetwork comprising frontal, temporal, insular, and parietal nodes are associated with current depression severity in MDD. Our results suggest possible recovery of white matter microstructure after an acute depressive episode.

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Compliance with ethical standards

Conflict of interest TK received unrestricted educational grants from Servier, Janssen, Recordati, Aristo, Otsuka, neuraxpharm. MW is scientific advisor of Avisoft Bioacoustics. This cooperation has no relevance to the work that is covered in the manuscript. The other authors declare no conflict of interest.

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