Association of brain white matter microstructure with cognitive performance in major depressive disorder and healthy controls: a diffusion-tensor imaging study

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INTRODUCTION
Cognitive deficits are central attendant symptoms of major depressive disorder (MDD) with a crucial impact in patients’ everyday life. Thus, it is of particular clinical importance to understand their pathophysiology. The aim of this study was to investigate a possible relationship between brain structure and cognitive performance in MDD patients in a well-characterized sample. N = 1007 participants (N_{MDD} = 482, healthy controls (HC): N_{HC} = 525) were selected from the FOR2107 cohort for this diffusion-tensor imaging study employing tract-based spatial statistics. We conducted a principal component analysis (PCA) to reduce neuropsychological test results, and to discover underlying factors of cognitive performance in MDD patients. We tested the association between fractional anisotropy (FA) and diagnosis (MDD vs. HC) and cognitive performance factors. The PCA yielded a single general cognitive performance factor that differed significantly between MDD patients and HC (P < 0.001). We found a significant main effect of the general cognitive performance factor in FA (P_{FWE} = 0.002) in a large bilateral cluster consisting of widespread frontotemporal-association fibers. In MDD patients this effect was independent of medication intake, the presence of comorbid diagnoses, the number of previous hospitalizations, and depressive symptomatology. This study provides robust evidence that white matter disturbances and cognitive performance seem to be associated. This association was independent of diagnosis, though MDD patients show more pronounced deficits and lower FA values in the global white matter fiber structure. This suggests a more general, rather than the depression-specific neurological basis for cognitive deficits.

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consistent with the brain’s architecture [22]. One possible measure of the microstructure of interconnecting fibers is diffusion-tensor imaging (DTI), a noninvasive, affordable, and efficient measurement to estimate fiber microstructure, reflecting myelination, axon density, axon diameter, and the number of fibers [23, 24]. White matter microstructure assessed by means of DTI has shown strong associations with cognitive performance in multiple studies in healthy controls (HC) and patient groups. In HC, cognitive performance measures were linked to cognitive deﬁcits of MDD patients has attracted less attention, albeit MDD patients to perform worse on cognitive tests. These deﬁcits were already shown for a wide range of disorders, e.g., stroke [30], Parkinson’s disease [31], small-vessel disease [32], multiple sclerosis [33], diabetes [34], substance abuse [22], schizophrenia [35, 36], or bipolar disorder [37]. However, the role of white matter integrity regarding cognitive deﬁcits of MDD patients has attracted less attention, albeit MDD patients were associated with reductions in ﬁber microstructure in the IFOF, the uncinate fasciculi (UF), the thalamic radiation (TR), the corticospinal tract (CT), and the inferior longitudinal fasciculi (ILF) and the SLF, the CB, and the CC compared with HC [38–41] and changes in the white matter connectome [42, 43].

Unfortunately, studies investigating the association between these microstructural abnormalities and cognitive deﬁcits in MDD are sparse: In geriatric depression, associations between cognitive deﬁcits and brain microfiber structure were found in overall prefrontal white matter, the CC, the TR, and the UF [44–46]. However, we are not aware of a study investigating white matter disturbances using DTI over the entire age and severity range of MDD patients.

Table 1. Descriptive statistics of the sample used in this study.

|                        | MDD (N = 482) | HC (N = 525) | Test statistic | P value | Cohen’s d |
|------------------------|--------------|-------------|----------------|---------|-----------|
| Age, M ± SD            | 37.12 ± 13.47| 31.68 ± 11.87| t(962.3) = −6.77a | <0.001 | 0.436     |
| Sex, f/m               | 311/171      | 321/204     | χ²(1) = 1.23b   | 0.268   | –         |
| IQMVT, M ± SD          | 113.79 ± 13.71| 114.98 ± 13.72| t(1005) = 1.38c | 0.170   | 0.087     |
| Education years, M ± SD| 13.15 ± 2.76 | 13.98 ± 2.42 | t(1005) = 5.05d | <0.001 | 0.329     |
| BDI Sum, M ± SD        | 17.99 ± 11.19| 2.50 ± 2.15  | t(505.68) = −29.68a | <0.001 | 2.640     |
| TMT-A, M ± SD          | 26.16 ± 10.36| 22.52 ± 8.40| t(927.0) = −6.10a | <0.001 | 0.401     |
| TMT-B, M ± SD          | 57.12 ± 24.30| 46.89 ± 17.30| t(861.5) = −7.64a | <0.001 | 0.521     |
| DSST, M ± SD           | 55.97 ± 12.17| 65.45 ± 11.05| t(973.2) = 12.9a  | <0.001 | 0.827     |
| RAVLT-S, M ± SD        | 55.73 ± 9.87 | 60.15 ± 8.27 | t(941.7) = 7.68a  | <0.001 | 0.501     |
| RAVLT-R, M ± SD        | 13.14 ± 2.99 | 13.90 ± 1.89 | t(799.2) = 4.75a  | <0.001 | 0.336     |
| CBTT-f, M ± SD         | 8.65 ± 1.84  | 9.44 ± 1.96  | t(1005) = 6.63c   | <0.001 | 0.418     |
| CBTT-b, M ± SD         | 8.04 ± 1.91  | 9.00 ± 1.71  | t(960.9) = 8.42a   | <0.001 | 0.541     |
| d2, M ± SD             | 168.05 ± 43.05| 194.00 ± 42.86| t(1005) = 9.58b    | <0.001 | 0.604     |
| LNS, M ± SD            | 15.83 ± 3.20 | 16.96 ± 3.09 | t(1005) = 5.70c    | <0.001 | 0.360     |
| VF-C, M ± SD           | 23.20 ± 6.01 | 25.45 ± 5.63 | t(1005) = 6.15a    | <0.001 | 0.388     |
| VF-P, M ± SD           | 11.32 ± 4.22 | 12.44 ± 4.41 | t(1005) = 4.11c    | <0.001 | 0.259     |
| VF-A, M ± SD           | 15.27 ± 3.48 | 16.90 ± 3.26 | t(1005) = 7.62c    | <0.001 | 0.481     |
| General Cognitive Performance factor, M ± SD | −0.37 ± 1.03 | 0.34 ± 0.84 | t(1005) = −12.04b | <0.001 | 0.935     |
| Number of hospitalizations, M ± SD | 1.66 ± 2.16 | –         | –              | –      | –         |
| Medication Load Index, M ± SD | 1.32 ± 1.43 | –         | –              | –      | –         |
| Comorbid diagnosis (yes/no) | 203/279 | –         | –              | –      | –         |

BDI Sum beck depression inventory, CBTT-f/b Corsi block-tapping test, forwards/backwards, d2 d2 test of attention, DSST digit substitution test, HC healthy control, IQMVT Intelligence quotient evaluated with the multiple-choice vocabulary test version B (dt. “Mehrfachwahl-Wortschatz-Test Version B”), LNS letter–number–sequences test, M mean, MDD major depressive disorder, RAVLT-S/B Rey Auditory Verbal Learning Test, sum of all correct words/recognitions, SD standard deviation, TMT-A/B trail making test, Version A/B, VF-C/P/A verbal ﬂuency test, category/phonemic/alternating.

aTwo-sample t test assuming unequal variance, bPearson χ² test, cTwo-sample t test assuming equal variance.

Another open question is the specificity of these potential alterations in MDD. The aim of this study was, thus, to the extent of previous results to the entire severity spectrum of MDD patients and to compare the association between fiber microstructure and cognitive deﬁcits with HC. First, we expect MDD patients to perform worse on cognitive tests. These deﬁcits should decline, but still be detectable in remitted patients (hypothesis 1). Second, we expect that MDD patients have lower microstructure compared with HC in the IFOF, the UF, the TR, the CT, the SLF and the ILF, the CB, and the CC (hypothesis 2).

Further, as associations between white matter microstructure and cognitive deﬁcits were already shown for a wide range of disorders, we do not expect that the association of cognitive test measures and white matter integrity is restricted to MDD patients. Rather, we would assume that the magnitude of the association between white matter and cognitive functioning should be similar between MDD patients and HC (hypothesis 3).

MATERIALS AND METHODS

Participants
N = 1007 participants (MDD: N = 482, M_age = 37.12, 311♀, HC: N = 525, M_age = 31.68, 321♀, Table 1, Supplement 1) were selected from the FOR2107 cohort assessed at two scanning sites—Marburg and Münster (the general description of the study [47] and the magnetic resonance imaging (MRI) quality-assurance protocol [48] are provided elsewhere). Participants were recruited through newspaper advertisements or in psychiatric hospitals. The FOR2107 cohort was approved by the Ethics Committees of the Medical Faculties, University of Marburg and University of Münster. All experiments were performed in accordance with the ethical guidelines and regulations. All participants gave written informed consent prior to

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examination. They received financial compensation for participation after the testing session.

Trained personnel confirmed psychiatric diagnoses or the lack thereof using the Structural Clinical Interview for DSM-IV-TR (SCID-IV) [49]. MDD patients were considered if they reported a current or lifetime diagnosis of MDD (severe, moderate, mild, (partially) remitted episode). Remission was defined as the absence of DSM-IV-TR diagnostic criteria for a MDD episode for at least two months at the time of the interview. Partial remission classified patients with subclinical symptoms (i.e., symptoms are insufficient to fulfill the diagnostic criteria of an MDD episode but severe enough to interfere with daily functioning) or if the time of recovery was shorter than 2 months.

Questionnaires, tests, and other clinical characteristics

In the FOR2107 cohort, all patients underwent neuropsychological testing in five subdomains of cognition: (1) executive functioning and sustained attention, 2) long and short-term memory performance, 3) visuospatial working memory, (4) verbal working memory, and (5) semantic processing. For a detailed description of the neuropsychological test battery, see Supplement 2. The general intelligence quotient (IQMVT) was estimated with the German version of the multiple-choice vocabulary intelligence test (MVT). Participants provided their highest educational degree. Education years were then estimated according to the typical time it takes to acquire the said degree.

To correct for typical clinical characteristics associated with MDD the following questionnaires and scores were used: The Beck Depression Inventory (BDI) [50] to assess current symptomatology, the number of prior hospitalizations provided by the participants in an interview, the cognitive component analysis were analyzed using IBM SPSS Statistics 26 (SPSS Inc., Chicago, IL, USA).

Analyses 2 and 3: diffusion-tensor imaging

The DTI data acquisition, quality-assurance protocol, and preprocessing steps have already been published [38]. Detailed information can be found in Supplements 3. Analysis was performed with FSL5.0.10 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/, Supplement 3). To test for statistical significance, the nonparametric permutation testing implemented in FSL’s “randomize” [59] was used with 5000 permutations. Using the default options optimized for TBSS, threshold-free cluster enhancement (TFCE) was used to correct for multiple comparisons.

Results

Differences between MDD and HC in cognitive performance. GCP differed significantly between MDD patients and HC (F(1,1001) = 74.46, P < 0.001, η² = 0.069) with a medium sized effect even after taking age, sex, IQMVT and education years into account. More precisely, acute and (partially) remitted MDD patients differed from HC in their GCP (F(1,1001) = 34.40, P < 0.001, η² = 0.033, Fig. 1). Post hoc Bonferroni corrected tests revealed that HC differed from acute (P < 0.001, 95% confidence interval (CI): [0.67, 1.06]), partially remitted (P < 0.001, CI: [0.42, 0.91]) and completely remitted MDD patients (P < 0.001, CI: [0.25, 0.73]), respectively. Acute MDD patients presented with lower GCP compared with completely remitted MDD patients (P = 0.002, CI: [−0.64, −0.10]), but not compared with partially remitted MDD patients (P = 0.300, CI: [−0.48, 0.07]). Lastly, the difference between partially and completely remitted MDD patients was not significant (P = 0.877, CI: [−0.48, 0.14]). Likewise, GCP was negatively associated with depression severity (BDI) in the MDD subsample after controlling for age, sex, IQMVT, and education years (F(1,469) = 48.2, P = 0.029, η² = 0.070; b = −0.007).

Prior to the inclusion of GCP in the model, the effect of diagnosis on FA was not significant (P = 0.072). Significant effects were found for AD, but not in MD and RD (Supplement 2). However, when including only acute MDD patients and HC, a main effect of diagnosis was found in FA (P = 0.018, k = 15,111 voxels in three clusters, MINI-coordinates of the peak voxel from the largest cluster: x = 34, y = −18, 36, Fig. 2) in all eight anticipated fiber bundles (Supplementary Table 2).
Analysis 3. ANCOVA including the general cognitive performance (GCP) factor

After including GCP into the model, neither the main effect of diagnosis ($P_{\text{FWE}} = 0.264$) nor a diagnosis × GCP interaction ($P_{\text{FWE}} = 0.365$) could be found for FA, while a significant main effect of diagnosis was still present for AD (Supplement 5). However, we found a significant main effect of GCP ($P_{\text{FWE}} = 0.002$, $k = 43,700$ voxels in one cluster, MNI-coordinates of the peak voxel: $x = 31$, $y = -66$, $z = 11$, Supplementary Table 3, Fig. 3) in a large bilateral cluster consisting of the CC, the IFOF, the anterior TR, and the SLF and ILF among other regions (Supplementary Table 2). Even after excluding (partially) remitted MDD patients to reduce variance and enhance differences with HC, this association between FA and GCP remained (Supplement 7). To verify that results were independent of the MRI scanner, two ANCOVAs with the mean FA values per participant from the significant cluster as the dependent variable were calculated in SPSS. This analysis confirmed that the GCP effect was present at both scanning sites, respectively (Marburg: $F(1,628) = 31.67$, $P < 0.001$, $\eta^2 = 0.048$, Münster: $F(1,361) = 12.93$, $P < 0.001$, $\eta^2 = 0.035$). As GCP and diagnosis are depending on each other, a linear ANCOVA might not be adequate to disentangle their effects. Thus, the analysis was repeated in SPSS using a nonparametric Generalized estimating equation (GEE) analysis. The results were confirmed using this method (main effect diagnosis: Wald-$\chi^2(1) = 0.29$, $P = 0.589$; main effect GCP: Wald-$\chi^2(1) = 25.95$, $P < 0.001$; interaction: Wald-$\chi^2(1) = 0.40$, $P = 0.528$). The tractography-based connectome analysis confirmed that the associations with GCP were widespread, including fibers...
cognitive deficits. This effect seems to be confined to white matter microstructure and not gray matter volume, as no positive associations were found between cognitive performance and gray matter structural MRI data.

These results highlight that intact fiber microstructure is associated with fast and accurate communication between brain regions required for optimal cognitive functioning [22]. Previous studies have already postulated that fine-tuned prefrontal signaling—with too much or too little signaling reducing cognitive performance—could be fundamental for sustained attention [61]. If the communicating fibers between frontal areas and other brain regions are structurally impaired, as hinted at by reduced FA in those fibers, this could result in cognitive impairment. It must be noted, however, that the results in this study seem to be regionally unspecific, as multiple tracts in a large bilateral cluster were affected.

Second, we found that MDD patients performed consistently worse on all cognitive tasks in concordance with previous analyses [2]. While these effects were found most strongly in tests assessing processing speed, a wide range of cognitive processes were affected in MDD patients, reflected by the single general cognitive performance factor extracted in the PCA. The differences between HC and acute or (partially) remitted MDD patients, respectively, support and extend the well-known report that cognitive deficits in MDD—while being alleviated—seem to persist in remission [14]. Deficits in cognitive performance could influence the inhibition of inappropriate behavioral or emotional processes, planning of future behavior, and flexible problem solving [14]. Cognitive deficits in remitted MDD patients may play a crucial role in sustaining psychosocial functioning—socially, mentally as well as in more general societal functions like workplace productivity. The neurobiological underpinnings of FA reductions associated with cognitive performance in MDD patients are most likely complex. It is possible, that interactive effects of genetic influences and environmental stressors might result in more pronounced fiber integrity reductions and, hence, elevated cognitive deficits in MDD [8, 62]. The variation in time of white matter maturation differs regionally. Especially association and commissural white matter fibers responsible for higher cognitive functioning, continue to develop throughout adolescence to early and middle adulthood [36, 63]. This prolonged development is the underlying basis for white matter plasticity, which in turn would be necessary for environmental and (epi-) genetic factors to in turn influence fiber structure [63–65].

Third, in contrast to our hypothesis, MDD patients’ FA differed only marginally from HC. Previous studies [35, 66] have already drawn into question that MDD patients’ microstructure differs from HC on a general basis. Choi et al. argued that small sample sizes, tracts prone to artifacts, or other aspects of MDD pathology (e.g., course of illness, childhood maltreatment experiences, antidepressant treatment, or specific symptoms) could have produced the significant differences between MDD patients and HC in earlier studies [66]. Likewise, the significant reduction in FA values in acute MDD patients (i.e., those who take more medication and experience more severe symptoms) compared with HC in our well-powered analysis suggests that the lifetime MDD diagnosis by itself might not be the sole driving force of white matter alterations in patients.

Acute MDD patients take more psychiatric medications and have a worse course of illness than (partially) remitted MDD patients in our sample, this could explain this difference.

Future studies might use the results of this study to use white matter morphological abnormalities associated with cognitive deficits in MDD to guide the inquiry of new therapeutic options. It should be investigated whether current treatment options for cognitive deficits in MDD [3, 8, 67, 68] like biobehavioral interventions (e.g., exercise, sleep hygiene, healthy diet), pharmacological treatments (e.g., vortioxetine), neurostimulation techniques (e.g., transcranial magnetic stimulation), and psychotherapeutic
CONCLUSION

Our findings highlight the importance of neurobiological wiring in cognitive performance in healthy controls and MDD patients. They provide robust evidence that global structural connectivity is associated with cognitive performance in MDD patients and HC. This association was independent of diagnosis, suggesting a general association between DTI measures of fiber integrity and cognitive performance. Efforts to treat cognitive deficits in MDD should, thus, consider the white matter as one of the underlying neural mechanisms.

REFERENCES

1. World Health Organization. International classification of diseases for mortality and morbidity statistics (11th Revision). 2018. Retrieved from https://icd.who.int/

2. Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. Psychological Med. 2014;44:2029–40.

3. Bortolato B, Carvalho A, McIntyre R. Cognitive dysfunction in major depressive disorder: a state-of-the-art clinical review. CNSNDST. 2015;13:1804–18.

4. Albert KM, Potter GG, McQuoid DR, Taylor WD. Cognitive performance in antidepressant-free recurrent major depressive disorder. Depression Anxiety. 2018;35:694–9.

5. Snyder HR. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. Psychological Bull. 2013;139:81–132.

6. Hartlage S, Alley LB, Vázquez C, Dykman B. Automatic and effortful processing in depression. Psychological Bull. 1993;113:247–78.

7. Dannlowski U, Kersting A, Arolt V, Lalee-Mentzel J, Donges U-S, Suslow T. Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. NeuroImage. 2008;42:1032–46.

8. Du J, Wang Y, Zhi N, Geng J, Cao W, Yu L, et al. Structural brain network measures are superior to vascular burden scores in predicting early cognitive impairment in post stroke patients with small vessel disease. Neurolmage Clin. 2017;2:1017-12.

9. Haghshomar M, Dolatshahi M, Ghazi Scharf F, Sanjani Moghadam H, Shrin Shandiz M, Aarabi MH. Disruption of inferior longitudinal fasciculus microstructure in Parkinson’s disease: a systematic review of diffusion tensor imaging studies. Front Neurol. 2018;9:598.

10. Moonen JF, Foster-Deleyne JC, van den Berg-Huijmans AA, Ruitjer W, de Craen AJM, van der Grond J, et al. Influence of small vessel disease and microstructural integrity on neuropsychological functioning in older individuals: The DANTE Study Leiden. Ajnr Am J Neuroradiol. 2017;38:2683–30.

11. van Schependom J, Gielen J, Laton J, Sotiropoulos G, Vanbinst A-M, Mey Jde, et al. The effect of morphological and microstructural integrity of the corpus callosum on cognition, fatigue and depression in mildly disabled MS patients. Magn Reson Imaging. 2017;40:109–14.

12. van Dijnkerken E, Ryan CM, Schoonheim MM, Barkhof F, Klein M, Moll AC, et al. Subgenual cingulate cortex functional connectivity in relation to depressive symptoms and cognitive functioning in type 1 diabetes mellitus patients. Psychosom Med. 2016;78:740–9.

13. Evans VC, Iversen GL, Yatham LN, Lam RW. The relationship between neurocognitive and psychosocial functioning in major depressive disorder: a systematic review. J Clin Psychiatry. 2014;75:1359–70.

14. Baune BT, Miller R, McAfoose J, Johnson M, Quirk F, Mitchell D. The role of cognitive impairment in general functioning in major depression. Psychiatry Res. 2010;176:183–9.

15. McIntyre RS, Xiao HX, Syeda K, Vinberg M, Carvalho AF, Mansur RB, et al. The prevalence, measurement, and treatment of the cognitive dimension/domain in major depressive disorder. CNS Drugs. 2015;29:577–89.

16. Gonda X, Pompili M, Serafini G, Carvalho AF, Rihmer Z, Dome P. The role of cognitive dysfunction in the symptoms and remission from depression. Ann Gen Psychiatry. 2015;14:27.

17. Vincent-Gil M, Keymer-Gausset A, Serra-Blasco M, Carceller-Sindreu M, Diego-Adelino J, de, Trujols J, et al. Cognitive predictors of illness course at 12 months after first-episode of depression. Eur Neuropsychopharmacol. 2018;28:529–37.

18. Keilp JG, Sackeim HA, Brodsky BS, Oquendo MA, Malone KM, Mann JN. Neuropsychological dysfunction in depressed suicide attempters. Am J Psychiatry. 2015;172:1677–87.

19. Kessing LV. Cognitive impairment in the euthymic phase of affective disorder. Psychopathology. 2012;45:107–13.

20. Joo E, Kim Y, Park J, Kim Y, Park J, Kim Y, et al. The association between cognitive impairment and remission in bipolar disorder: a systematic review and meta-analysis. J Affect Disord. 2013;147:116–22.

21. Varefu-Peters M, Jarvela K, Valtonen H, Lepola S, Lehtinen R, et al. White matter integrity in patients with newly diagnosed or recurrent major depressive disorder: a diffusion tensor imaging study. J Affect Disord. 2017;213:109–18.

22. Siegel SL, Sedrakyan A, Maris RM, Keesey K, Joffe RT, et al. The association between cognitive impairment and remission in bipolar disorder: a systematic review and meta-analysis. J Affect Disord. 2017;231:163–70.

23. Winston GP. The physical and biological basis of quantitative parameters derived from diffusion MRI. Quant Imaging Med Surg. 2012;2:254–65.

24. Le Bihan D. Looking into the functional architecture of the brain with diffusion MRI. Nat Rev Neurosci. 2003;4:469–80.

25. Grumbach P, Opel N, Martin S, Meinert S, Leeber EJ, Redlich R, et al. Sleep duration is associated with white matter structure and cognitive performance in healthy adults. Human Brain Mapping. 2020;41:397–405.
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