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Cognitive performance and brain structural connectome alterations in major depressive disorder

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Original Article

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Abstract

Background. Cognitive dysfunction and brain structural connectivity alterations have been observed in major depressive disorder (MDD). However, little is known about their interrelation. The present study follows a network approach to evaluate alterations in cognition-related brain structural networks.

Methods. Cognitive performance of $n = 805$ healthy and $n = 679$ acutely depressed or remitted individuals was assessed using 14 cognitive tests aggregated into cognitive factors. The structural connectome was reconstructed from structural and diffusion-weighted magnetic resonance imaging. Associations between global connectivity strength and cognitive factors were established using linear regressions. Network-based statistics were applied to identify subnetworks of connections underlying these global-level associations. In exploratory analyses, effects of depression were assessed by evaluating remission status-related group differences in subnetwork-specific connectivity. Partial correlations were employed to directly test the complete triad of cognitive factors, depressive symptom severity, and subnetwork-specific connectivity strength.

Results. All cognitive factors were associated with global connectivity strength. For each cognitive factor, network-based statistics identified a subnetwork of connections, revealing, for example, a subnetwork positively associated with processing speed. Within that subnetwork, acutely depressed patients showed significantly reduced connectivity strength compared to healthy controls. Moreover, connectivity strength in that subnetwork was associated to current depressive symptom severity independent of the previous disease course.

Conclusions. Our study is the first to identify cognition-related structural brain networks in MDD patients, thereby revealing associations between cognitive deficits, depressive symptoms, and reduced structural connectivity. This supports the hypothesis that structural connectome alterations may mediate the association of cognitive deficits and depression severity.

Introduction

Major depressive disorder (MDD) is an affective disorder that has been considered one of the most debilitating diseases for the past three decades (James et al., 2018). Cognitive deficits, such as impaired concentration, attention, or decision-making contribute to this debilitation and are prevalent among MDD patients: In studies, up to 90% of patients report cognitive

deficits (Conradi, Ormel, & De Jonge, 2011), and up to 48% of patients are diagnosed with cognitive deficits (Gualtieri & Morgan, 2008; Schwert, Stohrer, Aschenbrenner, Weisbrod, & Schröder, 2019). In acute depression, patients exhibit impairments in the cognitive domains of executive functioning, processing speed, memory, and attention (Baune, Fuhr, Air, & Hering, 2014; Rock, Roiser, Riedel, & Blackwell, 2014), which negatively affect daily psychosocial functioning (Buist-Bouwman et al., 2008; Fried & Nesse, 2014; McIntyre et al., 2013) and treatment outcome (McLennan & Mathias, 2010). Even after remission, moderate impairments in the domains of executive functioning and attention persist (Baune et al., 2014; Rock et al., 2014), causing impairments, for example, in occupational contexts (Baune et al., 2010; Jaeger, Berns, Uzelac, & Davis-Conway, 2006). Due to these adverse effects, cognitive deficits represent a symptom of outstanding importance within the symptom profile of MDD. It is, thus, crucial to investigate the factors underlying their emergence. Aiming to identify one of these factors, in the present study, we investigated the relationship between neurobiological alterations and cognitive deficits in MDD. More specifically, we explored the association of alterations in structural connectivity, i.e. white matter fiber tracts, and cognitive performance in a large sample of MDD patients and healthy controls (HC).

Structural connectivity within the human brain can be investigated using neuroimaging techniques such as diffusion-weighted imaging (DWI). DWI captures the diffusion of hydrogen molecules (Basser, Mattiello, & LeBihan, 1994), allowing researchers to reconstruct white matter fiber tracts. The entirety of these fiber tracts, i.e. the brain's *connectome*, can then be analyzed using network analyses (van den Heuvel & Sporns, 2013). In these analyses, white matter fiber tracts are considered *edges* that connect *nodes*, i.e. gray matter brain regions. Moreover, researchers can infer the connectome's topology using graph metrics or identify subnetworks of edges associated with a given effect.

Previous studies that applied network analyses on the structural connectome identified subnetworks of edges characterized by reduced structural connectivity in MDD patients (Korgaonkar et al., 2011; Myung et al., 2016; Repple et al., 2020; Sacchet, Prasad, Foland-Ross, Thompson, & Gotlib, 2015). These findings are supported by studies showing widespread microstructural white matter alterations in MDD patients (Han et al., 2014; Jiang et al., 2017; Murphy & Frodl, 2011; van Velzen et al., 2020). Results from both network and microstructural analyses suggest that structural connectivity alterations are especially pronounced in acute compared to remitted depression (Repple et al., 2020, 2019).

Given all these findings, we hypothesize a link between cognitive deficits and structural connectome alterations in MDD. This hypothesis is based on the theory that cognitive functions emerge from a network of interacting brain regions rather than from individual brain regions alone (Lim & Helpern, 2002). Adopting this theory, cognitive deficits would likely be associated with alterations within cognition-related networks rather than alterations in individual brain structures. Empirically, our hypothesis is supported by studies showing associations between structural connectivity and cognitive performance in HC (Dhamala, Jamison, Jaywant, Dennis, & Kuceyeski, 2021; Wiseman et al., 2018; Zimmermann, Griffiths, & McIntosh, 2018) and patients suffering, for example, from multiple sclerosis, HIV, or traumatic brain injury (Jolly, Scott, Sharp, & Hampshire, 2020; Yang et al., 2021; Zhang, Cortese, De Stefano, & Giorgio, 2021). Beyond results from network analyses, our hypothesis is supported by results from analyses of white matter microstructure in HC (Bolandzadeh, Davis, Tam, Handy, & Liu-Ambrose, 2012; Grumbach et al., 2020) and neurological or psychiatric patients (Eijlers et al., 2018; Karlsgodt, 2016; Mettenburg, Benzinger, Shimony, Snyder, & Sheline, 2012; Mollison et al., 2017; Rizk et al., 2017; Welton, Kent, Constantinescu, Auer, & Dineen, 2015; Yamada et al., 2015). However, to our knowledge, no study utilized network analyses to investigate the association between cognitive performance and the structural connectome in MDD. Following our above hypothesis, network analyses could provide valuable insights into this relationship by identifying both the networks associated with cognitive performance and MDD-related alterations within these networks. In the present study, we, thus, compared the cognitive performance of MDD patients and HC and employed network analysis to investigate associations between cognitive performance and the structural connectome. We expected (1) significantly reduced cognitive performance in MDD patients compared to HC, especially in the domains of processing speed and executive functioning, which is particularly pronounced in acutely depressed patients; and (2) significant associations between brain structural networks and cognitive performance across the whole sample. In exploratory analyses, we evaluated the effects of acute depressive symptoms within these cognition-related subnetworks.

Materials and methods

Participants and behavioral measures

A total of $N = 1484$ participants were included in our analysis. Details on participants' demographic and clinical characteristics can be found in Table 1. The sample was part of the Marburg–Münster Affective Disorders Cohort Study [see Kircher et al. (2019) for a general study protocol and Vogelbacher et al. (2018) for an MRI quality assurance protocol]. Study procedures were approved by the ethics committees of the medical faculties of the universities of Marburg and Münster. Participants aged 18–65 were recruited in one of the two cities (Marburg or Münster, Germany) via newspaper advertisements or local psychiatric hospitals. All participants gave written informed consent before participation. The Structured Clinical Interview for DSM-IV-TR [Axis I: Mental Disorders, SCID-I (Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997)] was used by trained personnel to diagnose psychiatric disorders. Patients were included in our analysis if they were diagnosed with a current depressive episode (MDDa) or a history of depressive episodes in partial or complete remission (MDDr) according to SCID-I. HC were included if they had no current or history of psychiatric or neurological diseases. See our previous work (Repple et al., 2020) for details on exclusion criteria and online Supplement S1 for information regarding patients' medication and comorbidities.

Scores from 14 cognitive tests (see Fig. 1a) were included to assess the participants' cognitive performance. Please refer to online Supplement S2 for details on the cognitive tests. Current depressive symptom severity was assessed in all participants using the Hamilton Depression Rating Scale (Hamilton, 1986).

Acquisition and processing of MRI data

MRI data acquisition

Two MR scanners at the Universities of Münster and Marburg were used for MRI data acquisition (see online Supplement S3

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Table 1. Demographic and clinical characteristics of the sample

Variable	HC ($n = 805$)	MDDr ($n = 372$)	MDDa ($n = 307$)	Statistic	p value	Sig[1]
Sex (female:male)	519:286 (64:36%)	249:123 (67:33%)	196:111 (64:36%)	0.89	0.616	
Age	33.77 ± 12.68	36.6 ± 12.98	36.42 ± 13.26	18.668	<0.001	A, B
Years of education	13.96 ± 2.54	13.59 ± 2.76	12.8 ± 2.58	24.177	<0.001	A, B, C
HAMD	1.41 ± 2.17	5.67 ± 5.23	14.1 ± 6.37	994.713	<0.001	A, B, C
Age of onset		25.64 ± 12.05	26.65 ± 13.28	2.078	0.15	A, B, C
Depressive episodes		3.42 ± 5.42	4.45 ± 7.19	4.352	0.037	
Hospitalizations		1.28 ± 1.8	1.85 ± 2.09	15.192	<0.001	
Medication load index		0.97 ± 1.21	1.75 ± 1.5	37.146	<0.001	

Note. Except for sex, mean values and standard deviations are shown. Test statistics and p values were derived from ANCOVA or χ^2 tests. HAMD, Hamilton Depression Rating Scale (total score); HC, healthy controls; MDDa, patients with an acute episode of major depressive disorder; MDDr, MDD patients in symptomatic remission.
[1]Letters indicate significant (i.e. $p_{FDR} < 0.05$) differences in post-hoc t tests between HC and MDDa (A), HC and MDDr (B), or MDDa and MDDr (C).

and S4 for details on MRI data acquisition and preprocessing, respectively). We included a scanner-site variable in all connectome analyses to account for scanner differences (Vogelbacher et al., 2018).

Anatomical connectome reconstruction

Details on the reconstruction and quality control of the anatomical connectome are provided in online Supplements S5 and S6, respectively. Briefly, white matter connectivity strength between 114 cortical brain regions [depicted by the Cammoun subdivision of the Desikan-Killiany atlas (Cammoun et al., 2012; Desikan et al., 2006)] was reconstructed using CATO (de Lange & van den Heuvel, 2021). Each participant's network was stored in a connectivity matrix with rows and columns representing nodes, i.e. brain regions, and matrix entries representing edges, i.e. white matter fiber tracts. Edge connectivity strength was measured as the number of reconstructed streamlines between two nodes. Edges were included if they incorporated at least three reconstructed streamlines to balance the sensitivity and specificity of the resulting connectivity matrices (de Reus & van den Heuvel, 2013; Zalesky et al., 2016).

Estimation of global connectivity strength and connectome topology

We calculated three measures to assess the connectome's global connectivity strength: (1) the number of edges present based on the binarized connectivity matrix; (2) the mean connectivity strength within the connectome as the mean number of streamlines per edge present (i.e. based on the weighted connectivity matrix); (3) the total number of streamlines within a connectome. In addition, we included seven standard measures describing the topology of the unweighted connectome in our analysis, such as shortest path length, global efficiency, clustering, or small-worldness (Rubinov & Sporns, 2010). For details on these measures, we refer to online Supplement S7.

Statistical analysis

Python 3.7.9 (Van Rossum & Drake, 2019) was used to analyze the data and create the figures (see online Supplement S8 for all Python packages employed). Additionally, Matlab 2019b (MATLAB, 2019) was used to apply network-based statistics (NBS) (Zalesky, Fornito, & Bullmore, 2010). Network figures were created using Brain Data Viewer (Dwyer et al., 2017). If not stated otherwise, statistical tests were conducted at a two-sided significance level of $\alpha = 0.05$.

Analyses of cognitive performance

We calculated cognitive factors by applying an exploratory factor analysis (EFA) on the test scores to abstract from cognitive tests to cognitive domains. Details on the EFA can be found in online Supplement S9. In short, the adequacy of the data for conducting an EFA was evaluated using Bartlett's test and the Kaiser–Meyer–Olkin test. Then, the test scores of all participants were entered into the EFA, and the number of factors to be extracted was determined according on their eigenvalues (Kaiser criterion, Scree plot) and a parallel analysis (Horn, 1965). The cognitive factors were interpreted according to the factor loadings of the test scores. All subsequent analyses were conducted using these cognitive factors.

Analyses of covariance (ANCOVA) were employed to test our first hypothesis that there are cognitive deficits in MDD patients, entering the respective cognitive factor as the dependent variable and remission status (HC *v.* MDDr *v.* MDDa) as independent variable. Further, age, sex, and years of education were included as covariates of no interest as those are key variables for evaluating an individual's cognitive performance. In case of a significant remission status effect, FDR (Benjamini & Hochberg, 1995) corrected post-hoc t tests were applied to assess which of the groups drove the effect.

Analyses of associations between cognitive performance and the structural connectome

To test our second hypothesis that cognitive performance is associated with structural brain networks across the whole sample, we first conducted global-level analyses. To this end, we employed linear regressions testing the bivariate association between a global connectome measure and a given cognitive factor while correcting for age, sex, and scanner-site. The p values assigned to the cognitive factors were extracted and corrected for multiple comparisons based on the FDR. To evaluate whether HC, acutely depressed, and remitted MDD patients differed in these associations, in a second step, we additionally entered the remission status and the remission status × cognitive factor interaction effects into the above regressions. The respective p values were again corrected based on the FDR.

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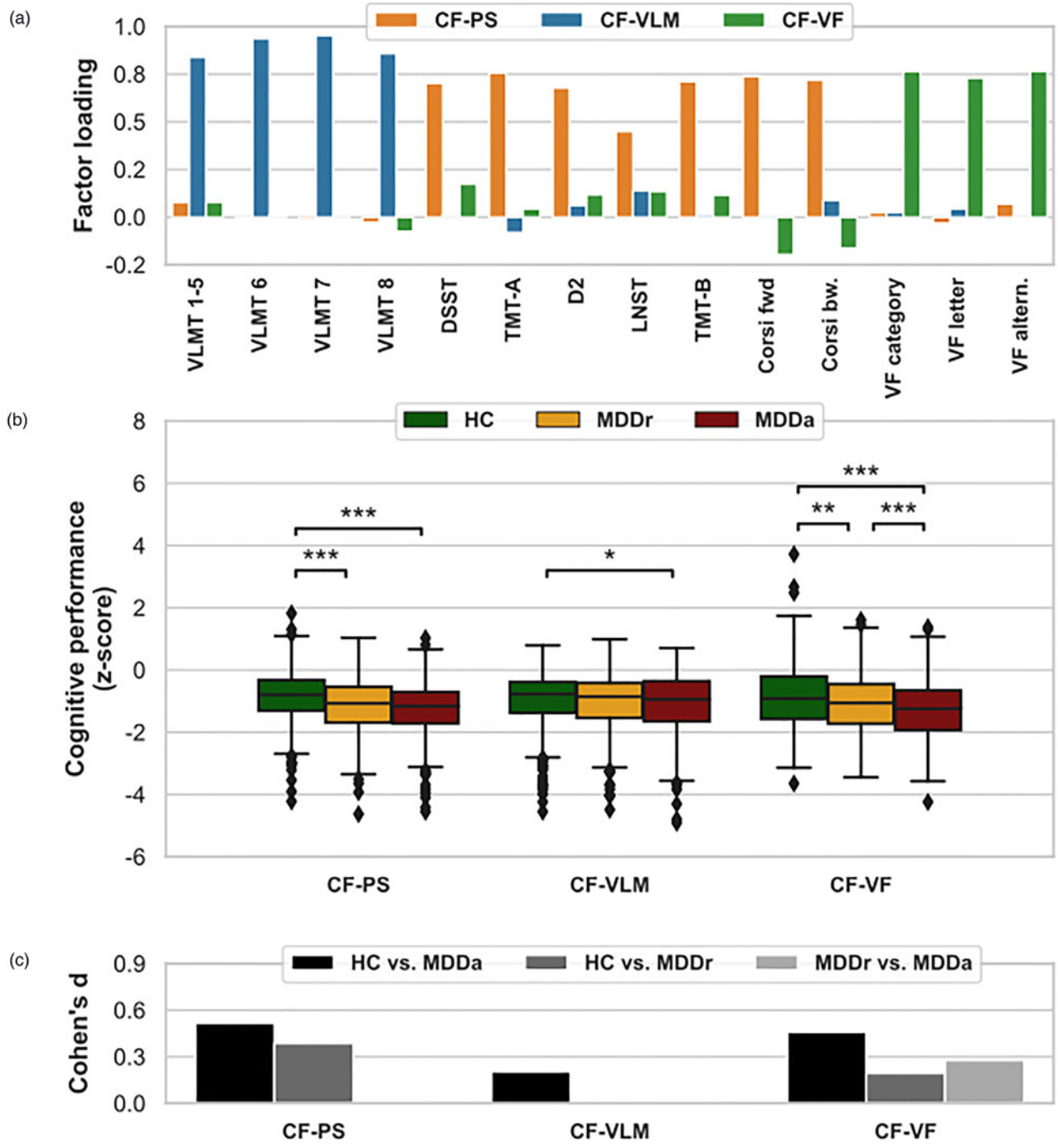

Fig. 1. Results from analyses on cognitive performance. (a) Factor loadings of cognitive test scores resulting from exploratory factor analysis. According to this analysis, three factors represent the variance within the cognitive performance of the sample: CF-PS, cognitive factor representing processing speed; CF-VLM, cognitive factor representing verbal learning and memory; CF-VF, cognitive factor representing verbal fluency; VLMT 1–5, verbal learning; VLMT 6, immediate verbal memory; VLMT 7, delayed verbal memory; VLMT 8, recognition; DSST, Digit Symbol Substitution Test; TMT, Trail Making Test; D2, D2 Test of attention; LNST, Letter Number Sequencing Test; Corsi fwd., Crosi Block-Tapping Test forward; Crosi bw., Corsi Block-Tapping Test backwards; VF category, semantic verbal fluency; VF letter, phenomic verbal fluency; VF altern., cognitive flexibility. (b) Differences in cognitive factors between healthy controls (HC) and patients with acute (MDDa) or (partially) remitted (MDDr) episode of major depressive disorder. *$p_{FDR} \leq 0.05$; **$p_{FDR} \leq 0.01$; ***$p_{FDR} \leq 0.001$. Boxes indicate the lower and upper quartile of the CF. Black lines within the boxes indicate the mean of the CF. Whiskers indicate the 1.5 inter-quartile range of the CF's lower and upper quartile. Diamonds indicate observations that fall outside this range. (c) Effect sizes (Cohen's *d*) representing these between-group differences. See online version for colored figures.

Next, to identify the subnetworks of edges underlying the cognition–connectome associations found at the global level, we employed NBS analyses in the whole sample (see online Supplement S10 for details). As for our global-level analyses, we chose a two-step approach for these local-level analyses: First, for each cognitive factor, an NBS analysis was conducted, which used family-wise error (FWE) corrected linear models to test the association between edge-wise connectivity strength (i.e.

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number of streamlines) and the respective cognitive factor while correcting for age, sex, and scanner-site. The significance of an identified subnetwork was assessed through permutation testing. To correct for multiple testing, we set the significance level to $\alpha = 0.05/\text{number of NBS analyses} = 0.05/3$ cognitive factors = 0.0167 in these analyses. Second, to evaluate whether remission status groups differed in these local-level associations, for each cognitive factor, an additional NBS analysis was conducted, testing the interaction effect of remission status and cognitive performance while correcting for the main effects of remission status, age, sex, and scanner-site. To correct for multiple testing, the significance level was again set to $\alpha = 0.0167$. Note that all subnetworks were obtained when applying an NBS F-threshold of $F = 5.8$. We chose this threshold because it is the highest at which subnetworks could be identified for all cognitive factors, allowing identification and comparison of the most specific subnetworks. See online Supplement S11 for analyses based on a more lenient threshold and online Supplement S12 for information on how different F-thresholds result in differing subnetwork sizes.

Analyses of effects of depression on identified subnetworks

Our analyses followed the hypothesis that comparable subnetworks are associated with cognitive performance in healthy and depressed individuals but that depressed individuals show alterations within these subnetworks. After identifying these subnetworks in our second analysis, in our third analysis, we assessed the effects of depression within the identified subnetworks by employing two complementary analyses that were based on the subnetwork-specific connectivity strength, i.e. the total number of streamlines in an identified subnetwork.

First, to evaluate whether depressed individuals show altered connectivity patterns within the identified subnetworks compared to HC, we entered the subnetwork-specific connectivity strength as the dependent variable into an ANCOVA with remission status (HC *v.* MDDr *v.* MDDa), age, sex, and scanner-site as independent variables. In case of a significant remission status effect, we applied post-hoc t tests to assess which of the groups drove the effect.

Second, we performed a correlation analysis to simultaneously test all associations forming the triad of acute depressive symptoms, cognition-related networks, and cognitive performance and to examine the influence of disease course characteristics on this triad. More specifically, we calculated correlations between (1) depressive symptom severity as measured by the Hamilton Depression Rating Scale (HAM-D), (2) subnetwork-specific connectivity strength, and (3) cognitive performance as measured by the cognitive factor used to identify the respective subnetwork. Correlations were calculated as partial correlations between two variables while holding the third constant and correcting for age, sex, and scanner-site. All p values were corrected for multiple comparisons based on the FDR. Next, to assess the influence of disease course characteristics on the triad, we repeated the correlational analyses while adjusting for age of disease onset, the number of depressive episodes or hospitalizations, or medication load (Opel et al., 2019; Redlich et al., 2014; Repple et al., 2020, 2017). Note that we focused this analysis on the MDD subgroup since most HC had no depressive symptoms (HAMD sum score $\leqq 2$ in 79% of HCs), resulting in a heavily skewed distribution of HAMD sum scores in HC. Moreover, all HC would have been excluded due to missing values in disease course characteristics. We opted for this correlational approach instead of mediation analysis as the assumption of causality necessary for mediation analyses cannot be verified using cross-sectional data (for exploratory mediation analysis with results in line with our approach, see online Supplement S13).

Results

Analyses of cognitive performance

Adequacy of the data for conducting an EFA was confirmed by Bartlett's test ($\chi^2 = 10\,567.97$, $p < 0.001$) and Kaiser–Meyer–Olkin test (KMO = 0.90). The EFA yielded three cognitive factors (see Fig. 1a for factor loadings). The first factor captured processing speed and lower executive functioning (CF-PS, explaining 41% of the variance), the second factor captured verbal learning and memory (CF-VLM, 13%), and the third factor captured higher executive functions, especially verbal fluency (CF-VF, 9%).

There were significant differences in cognitive performance between HC, MDDr, and MDDa in all three cognitive factors [CF-PS: $F_{(2,\ 1478)} = 79.09$, $p_{FDR} < 0.001$; CF-VLM: $F_{(2,\ 1478)} = 20.62$, $p_{FDR} < 0.001$; CF-VF: $F_{(2,\ 1478)} = 40.21$, $p_{FDR} < 0.001$]. Post-hoc t tests (see Fig. 1; see online Supplement S14 for test statistics) revealed that both MDDa and MDDr performed significantly worse than HC in processing speed and verbal fluency (all $p_{FDR} = 0.001$, $0.277 \leqslant d \leqslant 0.517$). In addition, MDDa performed significantly worse than HC in verbal learning and memory ($p_{FDR} = 0.019$, $d = 0.203$) and significantly worse than MDDr in verbal fluency ($p_{FDR} = 0.001$, $d = 0.277$). The latter remained significant when controlling for medication load, age of disease onset, or the number of depressive episodes or hospitalizations (see online Supplement S15). Besides, we tested for effects of patients' comorbidity on cognitive factors, which did not yield any significant results (see online Supplement S16). When outliers in cognitive factors were excluded, all but the differences between HC and MDDa in verbal learning and memory ($p_{FDR} = 0.067$) remained significant (see online Supplement S17)

Associations between cognitive performance and the structural connectome

Linear regression models revealed six significant associations between cognitive factors and global connectome measures. More specifically, all three cognitive factors were associated with the mean number of streamlines per edge (CF-PS: $t = 3.925$, $p_{FDR} = 0.001$, partial $\eta^2 = 0.010$; CF-VLM: $t = -3.925$, $p_{FDR} = 0.003$, partial $\eta^2 = 0.009$; CF-VF: $t = 3.047$, $p_{FDR} = 0.012$, partial $\eta^2 = 0.006$). Further, processing speed and verbal learning and memory were significantly associated with the total number of streamlines ($t = 4.102$, $p_{FDR} = 0.001$, partial $\eta^2 = 0.011$ and $t = -3.389$, $p_{FDR} = 0.008$, partial $\eta^2 = 0.004$) and verbal learning and memory was significantly associated with the non-normalized clustering coefficient ($t = -3.620$, $p_{FDR} = 0.003$, partial $\eta^2 = 0.009$). HC, acutely depressed, and remitted MDD patients did not differ in these associations as indicated by non-significant remission status × cognitive factor interaction effects (all $ps_{FDR} \geqslant 0.755$, see online Supplement S18).

NBS analyses conducted to identify the subnetworks underlying the global-level associations yielded the following results: For each cognitive factor, NBS identified a subnetwork of connections related to the respective factor (NBS F-threshold = 5.8, all $p_{FWE} \leqslant 0.014$, i.e. all $p_{FWE} \leqslant \alpha = 0.0167$, see Figs 2–4). These subnetworks comprised between 65 and 105 edges, which corresponds to 1.0% and 1.6% of the connectome. Connectivity

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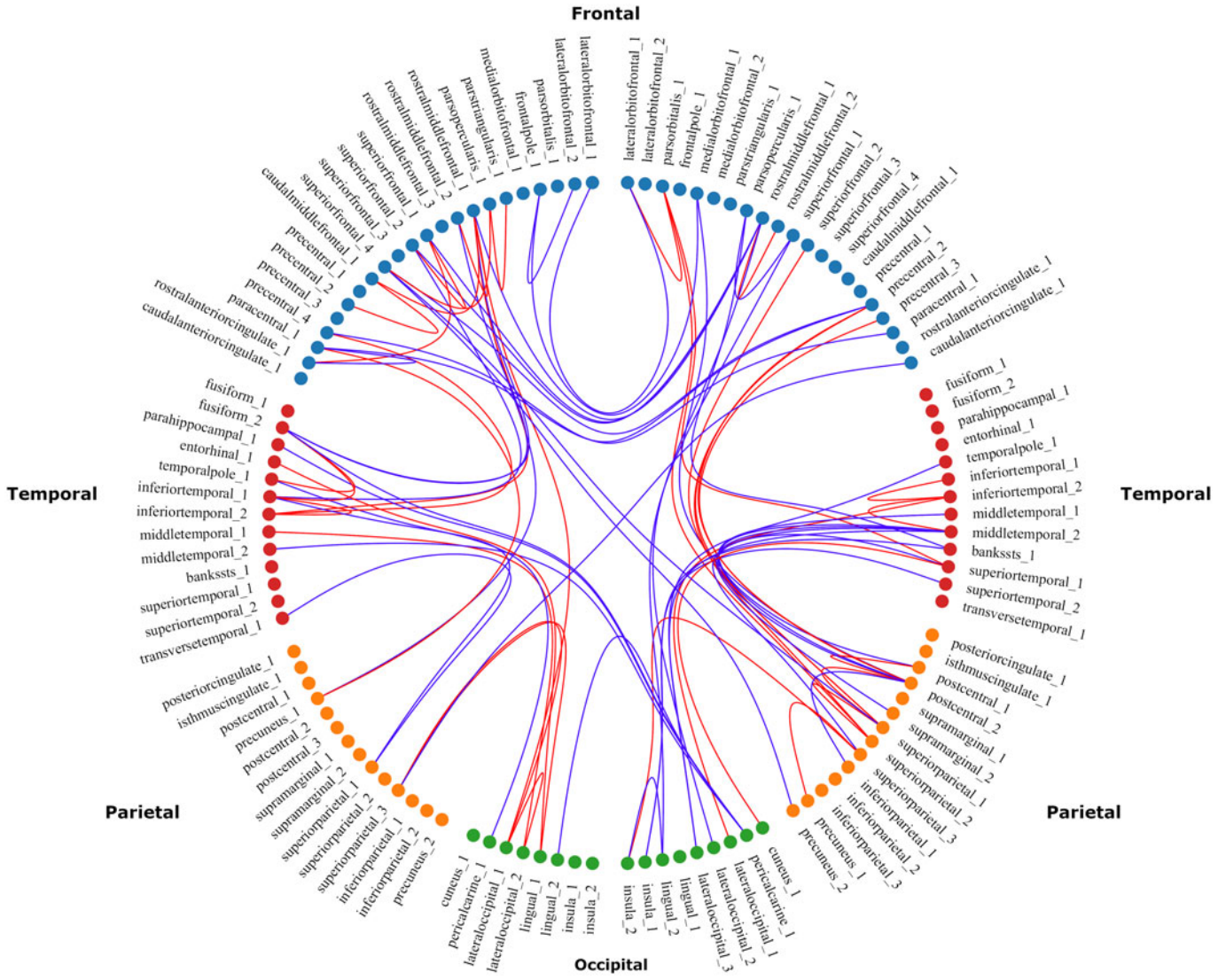

Fig. 2. Network of white matter tracts related to CF-PS performance. The figure shows the subnetwork of edges associated with the cognitive factor representing processing speed performance (CF-PS). The subnetwork was derived from network-based statistics (*F*-threshold = 5.8). Edges were positively (red) or negatively (blue) related to the cognitive factor (see online version for colored figures).

strength within the subnetworks identified for processing speed and verbal fluency was positively associated with the respective factor ($t = 8.939$, $p_{FDR} < 0.001$, partial $\eta^2 = 0.051$ and $t = 2.654$, $p_{FDR} = 0.008$, partial $\eta^2 = 0.005$, respectively). In contrast, connectivity strength within the subnetwork identified for verbal learning and memory was negatively associated with the factor ($t = -10.254$, $p_{FDR} < 0.001$, partial $\eta^2 = 0.066$). Notably, the pattern of structural connectivity differed across the subnetworks, as reflected by a low overlap of subnetwork edges (6–20%, see online Supplement S19). This is further supported by differences in the number of edges connecting frontal, temporal, parietal, and occipital brain regions: For example, the CF-PS network comprised a large proportion of fronto-frontal edges (26%). In contrast, the CF-VLM network was characterized by a core of temporo-parietal edges (25%). All subnetworks were equally distributed across left and right hemispheres, indicating comparable involvement of both hemispheres in the cognitive processes captured in the cognitive factors. See online Supplement S19 for further details.

In line with our global-level results, we did not identify any significant subnetworks associated with remission status × cognitive factor interaction effects (all $p_{FWE} \geqslant 0.070$, i.e. all $p_{FWE} > \alpha = 0.0167$, see online Supplement S18), suggesting that healthy and depressed individuals did not differ in the association of cognitive performance and local connectivity strength.

Robustness checks of our NBS analyses revealed no significant associations between identified subnetworks and participants' years of education or head motion during MRI acquisition (all $ps \geq 0.162$). Moreover, neither the exclusion of outliers in cognitive factors nor the use of non-thresholded connectivity matrices for NBS analyses changed the overall pattern of our results (see online Supplement S20).

Effects of depression on identified subnetworks

ANCOVAs conducted to evaluate differences in structural connectivity patterns in acutely depressed and remitted MDD patients compared to HC yielded a significant remission status

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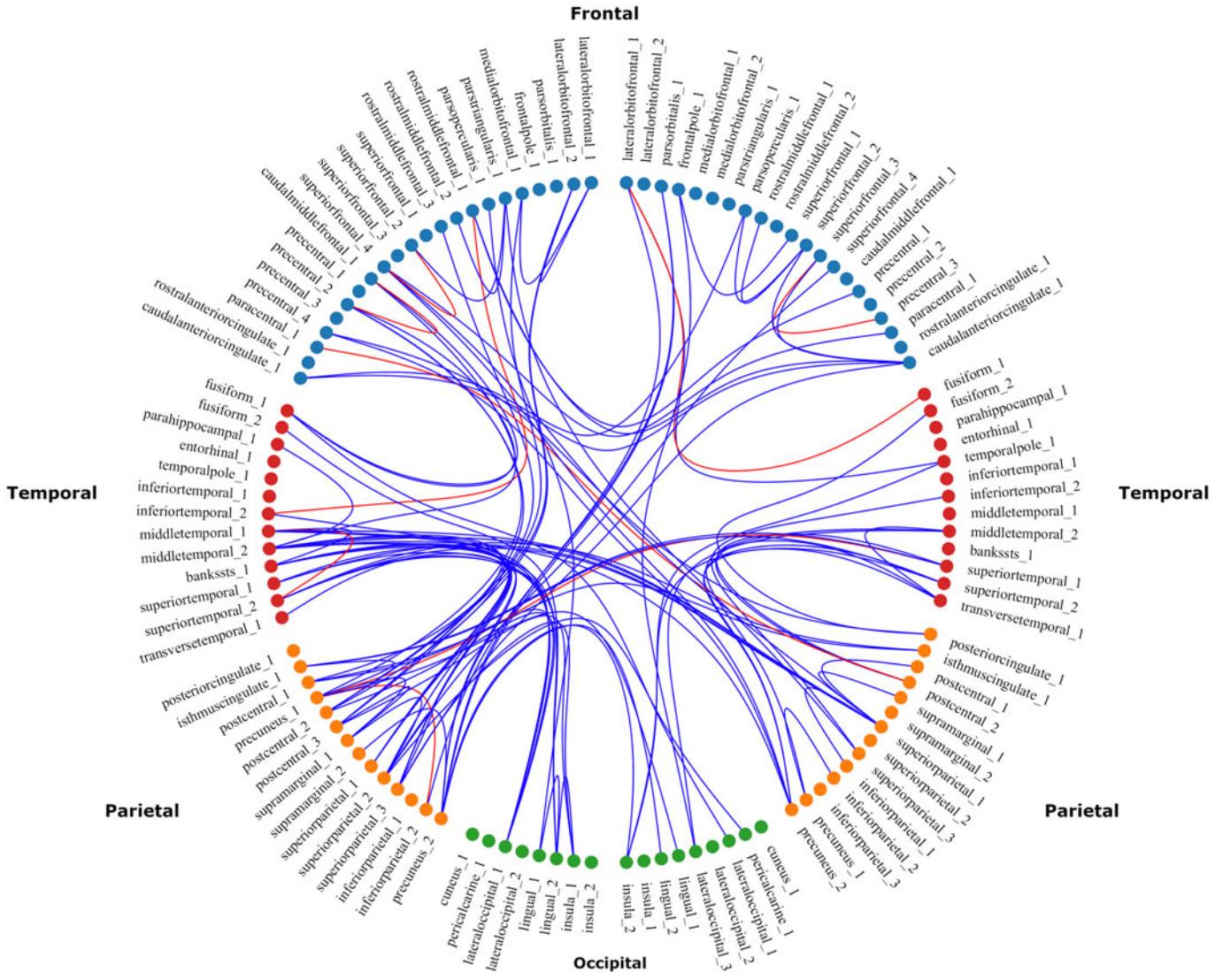

Fig. 3. Network of white matter tracts related to CF-VLM performance. The figure shows the subnetwork of edges associated with the cognitive factor representing verbal learning and memory (CF-VLM). The subnetwork was derived from network-based statistics (*F*-threshold = 5.8). Edges were positively (red) or negatively (blue) related to the cognitive factor (see online version for colored figures).

effect for the connectivity strength within the processing speed-related subnetwork [$F_{(2,\ 1477)} = 4.592$, $p_{FDR} = 0.031$]. Post-hoc *t* tests revealed a significantly reduced connectivity strength in MDDa compared to HC ($t = -3.032$, $p_{FDR} = 0.008$, $d = -0.200$).

Correlational analyses performed to examine the triad of (1) acute depressive symptoms, (2) cognitive performance, and (3) subnetwork-specific connectivity strength within MDD patients revealed that when considering all three variables simultaneously, all partial correlations remained significant only within the processing speed-related triad (see online Supplement S21 for all results). According to these correlations, higher processing speed was associated with higher subnetwork-specific connectivity strength independent of depression severity ($r_{CF-PS,NOS} = 0.201$, $p_{FDR} < 0.001$), while increased depressive symptoms were associated with reductions in both variables ($r_{HAMD,CF-PS} = -0.126$, $p_{FDR} = 0.002$, and $r_{HAMD,NOS} = -0.105$, $p_{FDR} = 0.006$, respectively). When controlling for current medication load, the correlation between processing speed and acute depressive symptom severity did not remain significant, which might be due to a substantial correlation between acute depressive symptoms and current medication load ($r = 0.390$, $p < 0.001$, see online Supplement S23). In contrast, controlling for measures of the previous disease course, such as the age of disease onset or number of hospitalizations or depressive episodes, did not change the significance of the association. Post-hoc analyses did not reveal significant associations to specific symptoms (see online Supplement S22), indicating that the association is driven more by cumulative symptom severity rather than a specific set of symptoms.

Discussion

The present study investigated the association between cognitive performance and the structural connectome of the brain in a sample of acutely depressed or (partially) remitted MDD patients and HC. Our analyses yielded three main results: First, we replicate findings demonstrating substantial cognitive deficits across various cognitive domains in MDD. Second, based on network analyses, we show a link between cognitive performance and the

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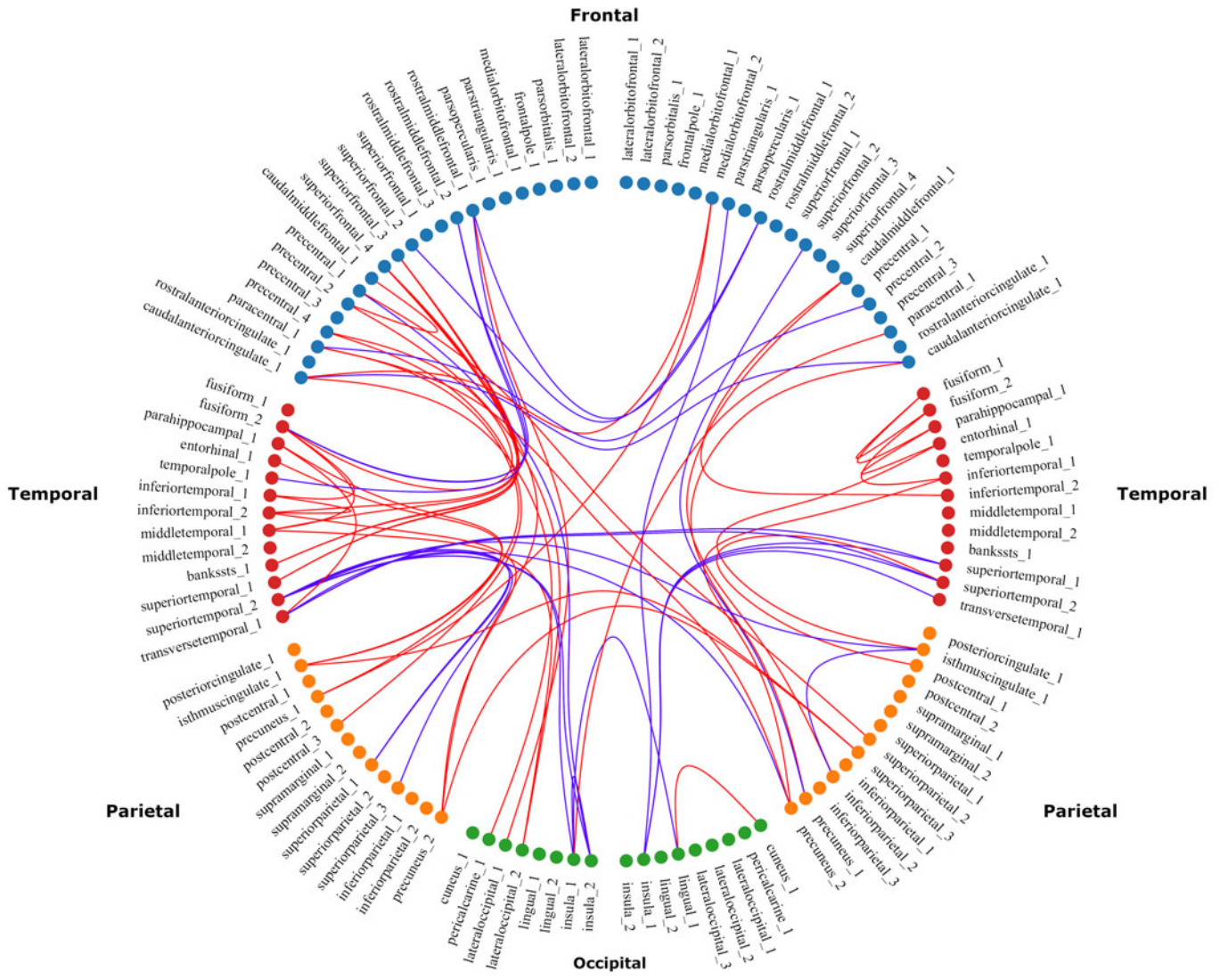

Fig. 4. Network of white matter tracts related to CF-VF performance. The figure shows the subnetwork of edges associated with the cognitive factor representing verbal fluency performance (CF-VF). The subnetwork was derived from network-based statistics (*F*-threshold = 5.8). Edges were positively (red) or negatively (blue) related to the cognitive factor (see online version for colored figures).

structural connectome and present evidence for domain-specific properties of that link. Notably, we found no evidence for differential cognition–connectome associations in healthy and depressed individuals. Instead, our analyses demonstrate structural connectome alterations *within* cognition-related subnetworks that may be a neurobiological factor underlying cognitive deficits in MDD.

We found widespread cognitive deficits in both MDDa and MDDr. The most pronounced effects were found in processing speed and verbal fluency. These results confirm our first hypothesis and align with previous meta-analytic findings (Rock et al., 2014). While our analyses are cross-sectional, they nevertheless support findings showing residual cognitive deficits in remitted MDD (Baune et al., 2014; Rock et al., 2014; Semkovska et al., 2019). Given the adverse effects of persistent cognitive deficits (Baune et al., 2014; Jaeger et al., 2006), their treatment should be of high priority. Although available drugs and remediation programs tend to improve cognitive deficits, meta-analyses also criticize the small number of primary studies (Motter et al., 2016; Prado, Watt, & Crowe, 2018; Rosenblat, Kakar, & McIntyre, 2015; Thérond et al., 2021). Therefore, future treatment research should consider the reduction of cognitive deficits as one of its primary goals.

Our analyses revealed associations between all three cognitive factors and the structural connectome, thus confirming our second hypothesis. Although we note the small effect sizes of the global-level associations, we also stress the more pronounced effects evident within the identified subnetworks. In our opinion, the fact that these effects are detectable even at the global level, albeit with small effect sizes, underscores the strength of the local-level effects rather than reducing the significance of our results. While few studies have analyzed the relationship between cognitive performance and the structural connectome (Jolly et al., 2020; Ponsoda et al., 2017; Zimmermann et al., 2018), our study extends their findings in several ways. First, our study is based on the largest sample to date, as it doubles the sample

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sizes of previous studies. Second, while previous studies identified several edges associated with cognitive performance, our study is the first to identify complete networks, which is more consistent with the hypothesis that cognitive functions emerge from a network of interacting brain regions (Lim & Helpern, 2002). In addition, to our knowledge, this is the first study to identify domain-specific networks of white matter fiber tracts. While we acknowledge that our cognitive factors might not fully generalize to other datasets, our analysis may nevertheless provide preliminary evidence for the domain specificity of the cognition–connectome link and elicit future studies on this issue.

All subnetworks comprised edges that are positively or negatively associated with cognitive performance, which aligns with previous findings (Zimmermann et al., 2018). However, while mean connectivity strength within the respective subnetworks was positively associated with processing speed and verbal fluency, verbal learning and memory was negatively associated with both global and subnetwork-specific connectivity strength. An explanation might be found in the cognitive processes represented by our cognitive factors: The cognitive tests related to the first two factors require quick information processing and responses, whereas the tests related to the verbal learning and memory factor mainly require retrieval of stored information. While processing of new information relies on white matter, as reflected by reduced processing speed in individuals with white matter damage (Chiaravalloti & DeLuca, 2008; Filley & Fields, 2016), retrieval of stored information rather depends on the gray matter (Hoffman et al., 2017), as evidenced by memory deficits in individuals with gray matter atrophy (Filley & Fields, 2016). Although both gray and white matter are essential for cognition in general, the divergence in the association of structural connectivity and cognition may, thus, reflect the differential contribution of white and gray matter to individual cognitive processes.

Our analyses provide evidence for substantial alterations within the processing speed-related subnetwork in depressed individuals. First, they reveal reduced connectivity strength in acutely depressed MDD patients compared to HC. This finding is complemented by analyses conducted within the MDD subgroup that demonstrate associations between structural connectivity, processing speed, and acute depressive symptom severity, independent of previous disease course characteristics. Of note, this relationship was not driven by a specific set of symptoms, but by the cumulative severity of all current depressive symptoms. To our knowledge, this is the first study to demonstrate these reciprocal associations based on a network approach. While we acknowledge that this pattern was found only for one of our three cognitive factors, we note that this factor captured by far the largest proportion of variance of the cognitive tests and was associated with the most severe cognitive deficits in MDD patients. Although the cross-sectional study design limits causal inferences, our results suggest that altered brain network communication may underlie the link between depression severity and cognitive deficits. This would support our hypothesis that cognitive deficits emerge from alterations in cognition-related networks rather than from alterations of individual brain structures. While we cannot address the neurobiological mechanisms underlying these alterations in our study, previous research might support speculation about the implication of inflammatory or stress-related processes. For instance, a possible mechanism of this interplay might be found in increased cortisol levels that have been related to depression, cognitive performance, and white matter alterations (Gomez et al., 2006; Keller et al., 2017; Li, Ruan, Chen, & Fang, 2021; Liu et al., 2016). It could be hypothesized that increased cortisol levels during progressing depressive symptoms lead to alterations in brain networks responsible for cognitive functioning, which in turn results in cognitive deficits.

Our study has several strengths and limitations. The main strengths are the variety of cognitive tests and the large sample covering a broad spectrum of MDD patients. The main limitation is the cross-sectional study design: Although our sample includes various remission states and thus provides an approximation of the impact of disease progression, longitudinal studies are needed to draw definitive conclusions on this question. Besides, cognitive factor labels might be subjective in that other researchers may have chosen different labels for the factors. However, it is crucial to separate the subjectivity of the factor labels from the subjectivity of the factor scores. Since their calculation was purely data-driven, we consider the scores largely objective.

To conclude, our findings emphasize the importance of cognitive deficits in depression. Moreover, our study substantially extends previous findings of a relationship between cognitive performance and the structural connectome by performing network analyses in the largest sample to date. By including MDD patients in these network analyses for the first time, our study provides preliminary evidence for an association between cognitive deficits, reduced connectivity in cognition-related subnetworks, and depressive symptoms, supporting the hypothesis that cognitive deficits in depression are associated with structural connectome alterations. Future research should verify this relationship in longitudinal studies and investigate possible neurobiological mechanisms underlying this association.

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