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# Brain Structural Network Connectivity of Formal Thought Disorder Dimensions in Affective and Psychotic Disorders

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## ABSTRACT

**BACKGROUND:** The psychopathological syndrome of formal thought disorder (FTD) is not only present in schizophrenia (SZ), but also highly prevalent in major depressive disorder and bipolar disorder. It remains unknown how alterations in the structural white matter connectome of the brain correlate with psychopathological FTD dimensions across affective and psychotic disorders.

**METHODS:** Using FTD items of the Scale for the Assessment of Positive Symptoms and Scale for the Assessment of Negative Symptoms, we performed exploratory and confirmatory factor analyses in 864 patients with major depressive disorder ($n$ = 689), bipolar disorder ($n$ = 108), or SZ ($n$ = 67) to identify psychopathological FTD dimensions. We used T1- and diffusion-weighted magnetic resonance imaging to reconstruct the structural connectome of the brain. To investigate the association of FTD subdimensions and global structural connectome measures, we employed linear regression models. We used network-based statistic to identify subnetworks of white matter fiber tracts associated with FTD symptomatology.

**RESULTS:** Three psychopathological FTD dimensions were delineated, i.e., disorganization, emptiness, and incoherence. Disorganization and incoherence were associated with global dysconnectivity. Network-based statistics identified subnetworks associated with the FTD dimensions disorganization and emptiness but not with the FTD dimension incoherence. Post hoc analyses on subnetworks did not reveal diagnosis × FTD dimension interaction effects. Results remained stable after correcting for medication and disease severity. Confirmatory analyses showed a substantial overlap of nodes from both subnetworks with cortical brain regions previously associated with FTD in SZ.

**CONCLUSIONS:** We demonstrated white matter subnetwork dysconnectivity in major depressive disorder, bipolar disorder, and SZ associated with FTD dimensions that predominantly comprise brain regions implicated in speech. Results open an avenue for transdiagnostic, psychopathology-informed, dimensional studies in pathogenetic research.

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Psychopathological syndromes, such as depressive, anxiety, or paranoid syndromes, are present in many psychiatric disorders (1–3). The question is whether their underlying brain correlates are diagnosis specific or instead syndrome specific. Deviations in speech, thought, and communication, clinically referred to as formal thought disorder (FTD), are usually implicated in schizophrenia (SZ) but are also ubiquitous in major depressive disorder (MDD), bipolar disorder (BD), and schizoaffective disorder, among others with varying degree and severity (4–9). Prevalence rates for FTD range up to 80% in patients with SZ and BD, 60% in patients with schizoaffective disorder, 53% in patients with MDD, and 6% in healthy individuals, which indicates that FTD exists on a continuum with normal speech (6). Both observational studies based on FTD ratings (5,7) and experimental and computational studies using natural language processing have highlighted alterations in language production measures in MDD, BD, and SZ (10–14). Examples are acoustic features (15,16), syntactic complexity (17,18), semantic coherence (19,20), speech connectedness (21), and analytical thinking (22). FTD is considered a marker of

 

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illness severity, social functional outcome, and rehospitalization (6,23–26).

Psychopathological factor analyses on FTD symptoms revealed 1 to 6 FTD domains, depending on the scale and population investigated (7,14,27–29). Only a few studies investigated transdiagnostic domains of FTD (2,7,9,13,30), however, highlighting the presence of FTD across affective and psychotic disorders. Previously, we have identified 3 psychopathological FTD factors across affective and psychotic disorders (i.e., disorganization, emptiness, and incoherence) (5), showing superior goodness of fit as compared with other models (29).

Yet, the neurocognitive, genetic, molecular, and brain structural and functional correlates of FTD remain under debate (4). It remains unclear whether particular FTD syndromes are associated with a similar brain network across different mental disorders. This finding would contribute to current attempts to identify neural and biological circuits underlying transdiagnostic symptoms of mental illness (31).

Research on the structural brain correlates of FTD in SZ demonstrated the gray matter volume (GMV) of not only the bilateral superior temporal gyri as a core region, but also the middle temporal gyri, inferior frontal gyri, and parietal lobe (32,33). Diffusion tensor imaging analyses have shown alterations in single white matter microstructure being associated with FTD in patients with SZ including the superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and uncinate fasciculus (34–38). Recently, we identified differential GMV correlates of FTD dimensions in a transdiagnostic sample. In this study, FTD was negatively associated with the GMV of the right middle frontal gyrus, left middle occipital/angular gyrus, and left hippocampus/thalamus, respectively (3,5). Furthermore, we were able to extend findings of single white matter microstructure associated with FTD in SZ in a recent transdiagnostic study to patients with MDD, BD, and schizophrenia spectrum disorders (5).

However, these studies focused on local alterations within, for example, specific white matter tracts instead of underlying white matter network-level alterations. Given the century-old debate on brain dysconnectivity and FTD (39), it is surprising that there is a complete lack of studies investigating associations between FTD and alterations in global macroscopic brain networks. Analyses of the brain's structural network, referred to as the structural connectome, can identify a subnetwork of brain regions (i.e., network nodes) connected by altered white matter fiber tracts (i.e., network edges).

Previous studies comparing patients with healthy control individuals indicated a network-level dysconnectivity not only in SZ (40), but also in MDD (41–44). Indeed, two transdiagnostic studies demonstrated altered central connections common to several disorders as well as a substantial overlap regarding patterns of dysconnectivity across affective and psychotic disorders (45,46). Yet, to date, no study has investigated if FTD is associated with this type of network-level dysconnectivity. Integrating the above findings of the prevalence of FTD across various psychiatric conditions (5,6) and the transdiagnostic patterns of connectome alterations (45–47), it is reasonable to take a transdiagnostic perspective when analyzing their association as well. Taking this perspective on FTD corresponds to the assumption that cognitive functions, including language production, as the behavioral measure of FTD, arise less from individual brain regions and more from a network of interacting areas (48). Consequently, dysfunctions such as FTD would more likely be associated with network-level alterations than with alterations in single brain structures. Following this assumption, the presence of FTD in an individual would be determined by the presence of network-level alterations, rather than their specific diagnosis, even if the severity of both connectome alterations and FTD might vary somewhat across different diagnoses, hence suggesting a continuous, transdiagnostic association between connectome alterations and FTD.

Therefore, the present study aimed to elucidate the association between FTD dimensions and the brain's structural white matter connectome across patients with MDD, BD, and SZ. We hypothesized that particular FTD syndromes are associated with specific alterations in brain structural subnetworks across diagnoses. These subnetworks, in turn, should comprise a substantial proportion of brain regions known from previous studies to be associated with FTD (e.g., the temporoparietal language junction). To test these hypotheses, we performed two complementary analyses. First, in an exploratory approach, we established the association between global (i.e., connectome-wide) white matter connectivity strength and FTD dimensions and identified those subnetworks within the connectome that drive the global-level associations. Second, in a confirmatory approach, we examined the degree to which the identified subnetworks (i.e., number of nodes) overlap with brain regions known to be associated with FTD from previous structural magnetic resonance imaging (MRI) studies.

## METHODS AND MATERIALS

### Participants

We included 864 patients with DSM-IV-TR MDD ($n$ = 689), BD ($n$ = 108), and SZ ($n$ = 67) (cf. Table 1) that were part of the MACS (Marburg-Münster Affective Disorders Cohort Study) of the FOR2107 cohort (49). Patients were recruited from the in- and outpatient departments of the respective universities as well as from other psychiatric services in the vicinity of Marburg and Münster. Patients with verbal IQ $<$ 80, history of head trauma or unconsciousness, current intake of benzodiazepines, and neurological illness were excluded from the study. All patients gave written informed consent to the study protocol before participation. All procedures were approved by the local ethics committees according to the Declaration of Helsinki.

### Psychopathology Assessment and FTD Dimensions

Patients underwent a semi-structured interview including the Structured Clinical Interview for DSM-IV-TR Axis I disorders (50), psychopathological scales, and further clinical information (e.g., number of hospitalizations, duration of episodes) (49). All interviewers were familiar and trained with the evaluation of clinical ratings. Interrater reliability was assessed with the interclass coefficient, achieving good reliability of $r > 0.86$ in all scales. FTD symptoms were assessed using the Scale for the Assessment of Positive Symptoms (51) and the Scale for the

**Table 1. Sample Characteristics, *N* = 864**

| | Major Depressive Disorder, *n* = 689 | Bipolar Disorder, *n* = 108 | Schizophrenia, *n* = 67 | Group Comparison, *p* (*F* or $\chi^2$) |
|---|---|---|---|---|
| Age, Years, Mean (SD) | 36.54 (13.11) | 41.31 (11.5) | 37.61 (10.92) | .001 (*F* = 6.61) |
| Sex, *n* | | | | <.001 ($\chi^2$ = 14.81) |
| Female | 451 | 61 | 29 | |
| Male | 238 | 47 | 38 | |
| TIV, $mm^3$, Mean (SD) | 1557.99 (145.47) | 1572.59 (142.35) | 1568.48 (150.14) | .546 (*F* = 0.61) |
| SANS Total Score, Mean (SD) | 7.55 (8.4) | 5.94 (7.88) | 15.58 (13.62) | <.001 (*F* = 27.49) |
| SANS Alogia Subscale, Mean (SD) | 0.49 (1.28) | 0.61 (1.43) | 2.33 (2.87) | <.001 (*F* = 43.44) |
| SAPS Total Score, Mean (SD) | 0.68 (2.08) | 2.38 (4.34) | 12.47 (13.71) | <.001 (*F* = 213.87) |
| SAPS Positive FTD Subscale, Mean (SD) | 0.36 (1.37) | 1.8 (3.38) | 3.61 (4.86) | <.001 (*F* = 43.44) |
| Antidepressants, *n* (%) | 412 (59.8%) | 46 (42.6%) | 15 (22.4%) | <.001 ($\chi^2$ = 42.39) |
| Antipsychotics, *n* (%) | 132 (19.2%) | 51 (47.2%) | 56 (83.6%) | <.001 ($\chi^2$ = 150.34) |
| Lithium, *n* (%) | 13 (1.9%) | 27 (25%) | 0 (0%) | <.001 ($\chi^2$ = 116.69) |
| Anticonvulsive, *n* (%) | 16 (2.3%) | 37 (34.3%) | 1 (1.5%) | <.001 ($\chi^2$ = 165.52) |
| Psychiatric Comorbidity, *n* (%) | 195 (28.3%) | 30 (27.78%) | 17 (25.37%) | .322 ($\chi^2$ = 2.27) |
| Age of Onset, Years, Mean (SD) | 26.14 (12.6) | 23.4 (10.72) | 23.05 (8.01) | .02 (*F* = 3.95) |

FTD, formal thought disorder; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; TIV, total intracranial volume.

Assessment of Negative Symptoms (52). In a previous study of ours (5), we calculated FTD dimensions, using the single items of the positive FTD and alogia subscales of the Scale for the Assessment of Negative Symptoms and Scale for the Assessment of Positive Symptoms (see Supplement Section S1). The current sample represents a subsample of our previous factor analysis (*N* = 1071) (5) from which, after quality checks of MRI measurements used, 207 individuals had to be excluded, leaving 864 participants for the current analyses.

## Acquisition and Processing of MRI Data

MRI data were acquired using 2 MR scanners at the Department of Psychiatry of the University of Marburg and the Institute for Translational Psychiatry of the University of Münster (see Supplement Section S2). To account for scanner differences and a body-coil change at the study site in Marburg, we included 2 dummy-coded variables in all analyses, representing 3 scanners.

## Anatomical Connectome Reconstruction

For a detailed account of our procedure for reconstructing the anatomical connectome, see Supplement Section S3. Briefly, we reconstructed the strength of white matter connectivity between 114 cortical brain regions (parceled according to the Cammoun subdivision of the Desikan-Killiany atlas) (53,54) using CATO (55). Each participant's anatomical connectome was then 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. The connectivity strength of an edge was measured as the number of the reconstructed streamlines incorporated within that edge. Edges were considered if they comprised at least 3 reconstructed streamlines to balance the sensitivity and specificity of the resulting connectivity matrices (56,57). Details of our quality control procedure for connectivity matrices can be found in Supplement Section S4.

## Calculation of Global Connectome Measures

We calculated 3 measures to assess the connectome's global connectivity strength: 1) the number of edges present in the binarized connectivity matrix; 2) the total number of streamlines within a connectome; and 3) the mean number of streamlines per edge present.

To assess whether FTD is associated with alterations across all hierarchical levels of the connectome, we categorized all edges in hierarchical classes by adopting the rich club perspective (58). Rich club organization of networks refers to the tendency for nodes with a high degree (i.e., a high number of connections of a given node with other nodes) to be more interconnected than expected based on their high degree alone (58). High-degree rich club nodes were defined as the top 15% of high-degree nodes for our analysis. Based on the categorization of network nodes into hub nodes and nonhub nodes, we individually classified all network edges into 1 of 3 classes: rich club connections (edges connecting hub nodes), feeder connections (edges connecting hub nodes to nonhub nodes), and local connections (edges connecting nonhub nodes). We calculated the connectivity strength for each of these classes as the subject-wise mean number of streamlines across all edges included in the respective class.

To assess associations between FTD and global connectome topology, we calculated standard graph theory–based measures of connectome segmentation and integration for each participant (see Supplement Section S5) (59). These included measures of segmentation, such as the clustering coefficient, quantify the connectome's tendency to form densely connected subnetworks. Measures of integration, such as the shortest path length or global efficiency, quantify the connectome's ability to aggregate information from

different subnetworks. Further, we included the ratios of both integration and segmentation, i.e., small-worldness.

### Statistical Analysis

We employed Python 3.7.9 (60) for analyzing the data and creating the figures (Supplement Section S6) and MATLAB 2019b (61) for applying network-based statistic (NBS) (62) and creating network figures (63). If not stated otherwise, statistical tests were conducted at a two-sided significance level of $\alpha = 0.05$.

Our statistical analysis included two complementary approaches. First, we followed an exploratory approach by establishing any associations 1) between FTD and measures of global (i.e., connectome-wide) connectivity strength and 2) between FTD and local subnetworks of white matter fiber tracts. Second, we followed a confirmatory approach by statistically comparing the subnetworks identified in our first approach with brain regions associated with FTD in previous studies (4,32,33).

### Exploratory Analyses on Associations Between FTD and Structural Connectivity

We employed two analyses to establish the relationship between white matter connectivity strength and FTD. In our first analysis, we utilized robust linear regression models (statsmodels' rlm-function) to test all bivariate associations between measures of global connectivity strength and each of the 3 FTD factors while correcting for age, sex, and scanner. If a given FTD factor was significantly associated with measures of global connectivity strength, we used the same model to assess if this global-level association could be replicated within rich club, feeder, or local edges. *p* Values depicting the significance of the associations were extracted from the regression models and corrected for multiple comparisons using the Benjamini-Hochberg procedure (64).

Our second analysis identified networks of white matter fiber tracts associated with FTD using NBS (62). NBS identifies a network-level effect by performing univariate mass tests at the edge level while controlling for familywise errors and correcting for covariates of no interest. The significance of an identified network is established using a permutation test (5000 permutations; see Supplement Section S7). Here, 3 NBS analyses were conducted, testing the association between edgewise connectivity strength and one of the FTD factors while correcting for age, sex, and scanner site. To evaluate the robustness of the identified networks, we 1) tested for significant associations between the identified networks and participants' head motion during MRI acquisition, 2) tested the associations while additionally correcting for total intracranial volume, and 3) repeated the NBS analyses based on non-thresholded connectivity matrices (Supplement Section S8). None of these approaches substantially changed the overall pattern of our results.

### Confirmatory Analyses on Identified Subnetworks Associated With FTD

In our second approach, we statistically compared the nodes of the identified subnetworks with brain regions that have been associated with FTD in previous structural MRI studies in patients with SZ (32,33), hereafter referred to as FTD brain regions. To this end, we first selected the set of FTD brain regions and mapped them to the brain parcellation specified by the Cammoun subdivision of the Desikan-Killiany atlas (Supplement Section S10). These regions were selected based on the following criteria: 1) listed in brain-structural FTD review/meta-analytic studies (32,33) and 2) reported in at least 3 independent original studies. This resulted in a selection of 24 FTD brain regions. We then calculated the overlap between the subnetworks identified with NBS and the FTD brain regions derived from previous studies as the proportion of nodes in a given subnetwork that are also FTD brain regions. The significance of this overlap was assessed through a permutation test. This test involved 1) randomly drawing a set of brain regions (corresponding to the number of nodes of the subnetwork in question) from the list of all 114 cortical brain regions specified by the Cammoun parcellation and 2) establishing the overlap between this randomly drawn set of brain regions and the FTD brain regions. This procedure was repeated 10,000 times to obtain a null distribution of chance-level overlaps. The significance of an overlap found between an identified subnetwork and the FTD brain regions was then calculated as the number of permutations in which the chance-level overlap was higher than the observed overlap. Consequently, the respective *p* values represent one-sided significance.

## RESULTS

### Exploratory Analyses on Associations Between FTD and Structural Connectivity

Robust linear regression models revealed significant negative associations between the 3 psychopathological FTD factors and both the total number of streamlines and the global mean number of streamlines per edge (see Table 2 for test statistics). These negative associations could be replicated at the highest and lowest levels of hierarchy of the connectome as indicated by negative associations of 2 of the 3 FTD factors (i.e., emptiness and incoherence) with the mean number of streamlines in rich club or local edges. After correcting for multiple comparisons, 3 negative associations remained significant: the total number of streamlines and emptiness, the global mean number of streamlines per edge and emptiness, and the mean number of streamlines in rich club edges and incoherence.

For the FTD factors of disorganization and emptiness, NBS successfully identified subnetworks of white matter fiber tracts that were negatively associated with the respective factor (all $p_{\text{familywise error}} < .05$; NBS t-threshold = 1.5; disorganization network: 47 nodes and 53 edges, $\eta_p^2 = 0.062$; emptiness network: 64 nodes and 74 edges, $\eta_p^2 = 0.060$) (see Figure 1). The network associated with incoherence did not reach significance ($p_{\text{familywise error}} = .093$).

Associations between both networks and the respective FTD factors remained significant when correcting for medication load or measures of disease severity such as the age of disease onset or lifetime cumulative duration of hospitalizations (see Supplement Section S11). Analyses of the regional distribution of the networks revealed differences in the proportion of frontal, temporal, parietal, and occipital brain regions

**Table 2. Associations Between FTD Factors and Global Connectome Measures**

| FTD Factor | Connectome Measure | $z$ | $p$ | $p_{FDR}$ | $\eta_p^2$ |
|---|---|---|---|---|---|
| Disorganization | Total number of present edges | −1.136 | .256 | .307 | 0.002 |
| | Total number of streamlines | −1.988 | .047 | .072 | 0.005 |
| | Global mean number of streamlines per edge | −2.055 | .040 | .072 | 0.005 |
| | Mean number of streamlines in rich club edges | −2.252 | .024 | .054 | 0.006 |
| | Mean number of streamlines in feeder edges | 0.182 | .855 | .855 | 0.000 |
| | Mean number of streamlines in local edges | −2.317 | .020 | .051 | 0.006 |
| Emptiness | Total number of present edges | −1.370 | .171 | .220 | 0.002 |
| | Total number of streamlines | −3.075 | .002 | .018[a] | 0.011 |
| | Global mean number of streamlines per edge | −3.414 | .001 | .018[a] | 0.013 |
| | Mean number of streamlines in rich club edges | −2.374 | .018 | .051 | 0.007 |
| | Mean number of streamlines in feeder edges | −1.715 | .086 | .119 | 0.003 |
| | Mean number of streamlines in local edges | −2.872 | .004 | .024[a] | 0.010 |
| Incoherence | Total number of present edges | −0.795 | .426 | .451 | 0.001 |
| | Total number of streamlines | −1.980 | .048 | .072 | 0.005 |
| | Global mean number of streamlines per edge | −2.334 | .020 | .051 | 0.006 |
| | Mean number of streamlines in rich club edges | −2.651 | .008 | .036[a] | 0.008 |
| | Mean number of streamlines in feeder edges | −0.924 | .355 | .399 | 0.001 |
| | Connectivity strength in local edges | −2.110 | .035 | .070 | 0.005 |

The table shows the associations between FTD factors and global connectome measures. Test statistics were derived from robust linear regression models correcting for age, sex, and scanner site. Both uncorrected $p$ values and $p$ values corrected for multiple comparisons using the Benjamini-Hochberg procedure ($p_{FDR}$) are listed.

FDR, false discovery rate; FTD, formal thought disorder.

[a]Significant result.

participating in the networks ($\chi^2_3 = 9.290$, $p = .003$). This difference was driven by a disproportionately low number of frontal nodes and a disproportionately high number of temporal nodes involved in the disorganization network (10.64% and 38.30%, respectively). Consequently, the disorganization network was particularly characterized by temporotemporal edges (26.4% of network edges). The emptiness network showed a largely proportional involvement of frontal, temporal, parietal, and occipital brain regions (see Supplement Section S12).

In a post hoc analysis, we extracted the edges included in the previously identified subnetworks for each participant to calculate the total number of streamlines within those subnetworks, considering this a measure of subnetwork-specific white matter connectivity strength. We then evaluated the influence of the participants' diagnosis on the association between subnetwork-specific connectivity strength and the FTD factor used to identify the subnetwork by testing for any diagnosis × FTD factor interaction effects. Importantly, these analyses did not reveal significant diagnosis × FTD factor interaction effects on the identified networks (disorganization network: $F_{2,854} = 0.340$, $p = .712$; emptiness network: $F_{2,854} = 0.066$, $p = .937$).

To evaluate the robustness of these null findings in more detail, we conducted two additional analyses (see Supplement Section S9). Because the frequentist statistic does not allow for interpretation of the null hypothesis (i.e., the absence of interaction effects), we repeated the analysis using Bayesian analyses of covariance to obtain Bayes factors (BFs) that quantify the evidence for the null hypothesis. These analyses revealed BFs below 1 (disorganization network: $BF_{10} = 0.002$; emptiness network: $BF_{10} = 0.002$), indicating that our data would have occurred substantially (i.e., $BF_{10} = 0.002$ times) less likely if interaction effects were present (i.e., $H_1$) than in their absence (i.e., the $H_0$).

To account for the unequal group sizes of patients with MDD, BD, and SZ in our sample, we evaluated the variability characterizing the interactions' effect sizes due to the proportion of patients with MDD, BD, and SZ included in the analysis. To this end, we applied a nonstratified 10,000-fold bootstrapping for the above $F$ values denoting the interaction effects. This approach revealed some variance characterizing the effect size of the interactions (disorganization network: 95% bootstrap CI, 0.030–3.666; emptiness network: 95% bootstrap CI, 0.014–1.961). Interestingly, this variation appeared to be primarily influenced by whether patients presented with FTD or not, rather than with their specific diagnosis of MDD, BD, or SZ.

## Confirmatory Analyses on Identified Structural Connectivity Correlates of FTD

After successfully identifying structural brain networks associated with FTD, we employed a confirmatory analysis in which we compared the nodes of those networks with 24 brain regions that have been associated with FTD in previous structural MRI studies in SZ. This analysis revealed a substantial proportion of nodes in both subnetworks that were found to be associated with FTD in previous studies (disorganization network: 18 out of 47 nodes; emptiness network: 18 out of 64 nodes) (see Figure 2). To evaluate the significance of this overlap with FTD brain regions, we conducted permutation

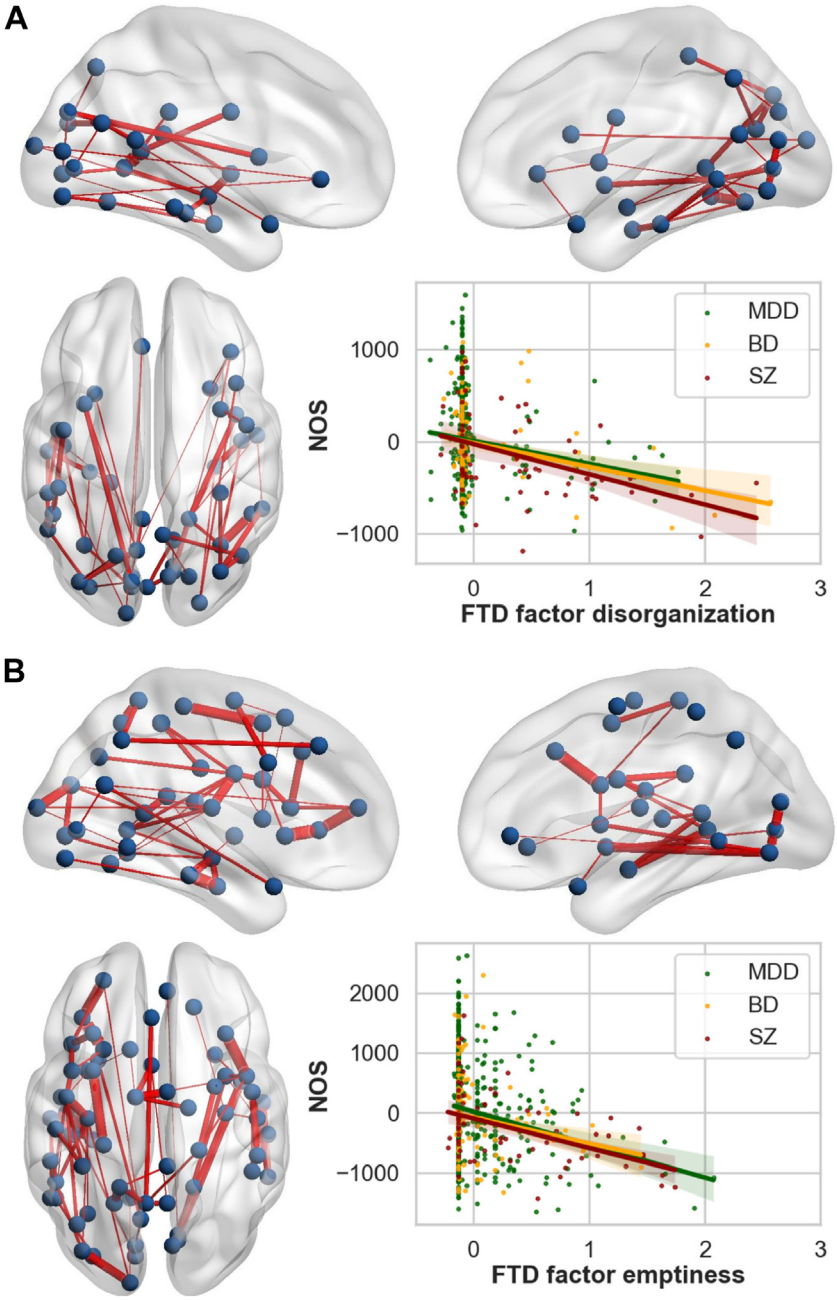


**Figure 1.** Networks of white matter fiber tracts associated with formal thought disorder (FTD) factors. Subnetworks of white matter fiber tracts associated with FTD factors disorganization and emptiness. In both subnetworks, connectivity strength (i.e., number of streamlines [NOS]) was negatively associated with the respective FTD factor across all patient groups. **(A)** Sagittal and dorsal views of the subnetworks associated with the FTD factor disorganization and regression plot depicting this association. **(B)** Sagittal and dorsal views of the subnetworks associated with the FTD factor emptiness and regression plot depicting this association. Subnetworks were identified using network-based statistic toolbox (corrected significance level: $p_{\text{familywise error}} < .05$, NBS t-threshold = 1.5) while correcting for age, sex, and scanner. Associations are depicted in partial regression plots corrected for age, sex, and scanner, thus resulting in negative NOS values. BD, bipolar disorder; MDD, major depressive disorder; SZ, schizophrenia.

tests comparing the overlaps found for the two networks to overlaps from 10,000 randomly selected sets of nodes of the same size. These tests indicated that the overlaps of the disorganization and emptiness networks with FTD brain regions (18 out of 47 and 18 out of 64, respectively) were significantly higher than would be expected for a randomly selected set of nodes (mean overlap with FTD brain regions in permutation test for disorganization network: 9.89 nodes; 95% CI, 9.85–9.93; $p < .001$; mean overlap with FTD brain regions in permutation test for emptiness network: 13.44 nodes; 95% CI, 13.40–13.48; $p = .009$), suggesting that both networks indeed comprised disproportionately high numbers of brain regions known from previous studies to be associated with FTD in SZ.

## DISCUSSION

To the best of our knowledge, this is the first study to investigate the association between FTD symptom dimensions and network-level structural connectivity, measured with diffusion

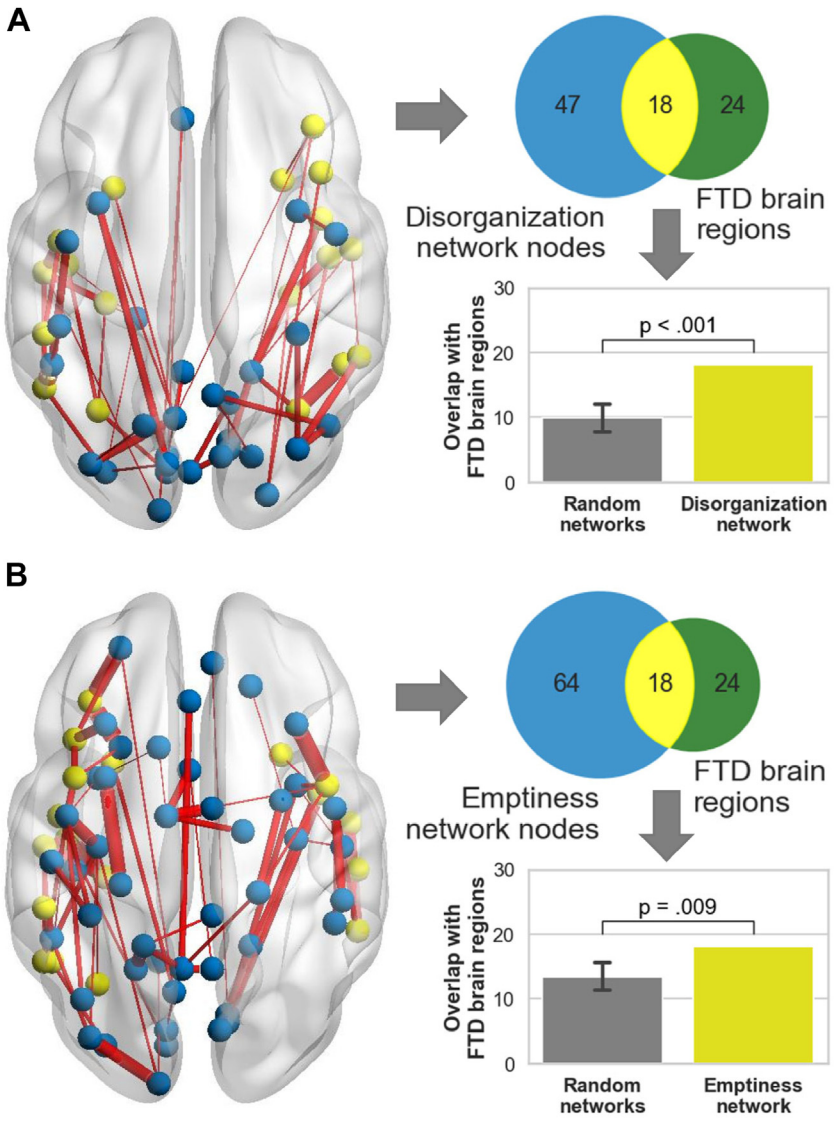


**Figure 2.** Overlap of identified networks with brain regions associated with formal thought disorder (FTD) in previous studies of patients with schizophrenia. **(A)** Disorganization and **(B)** emptiness networks in dorsal views. Both networks comprise a substantial number of nodes (yellow) (18 out of 47 and 18 out of 64, respectively) that have been associated with FTD in previous structural magnetic resonance imaging studies investigating FTD in schizophrenia (32,33). For both networks, the number of those nodes was significantly higher than for randomly selected networks of the same size (10,000 permutations).

tensor imaging, across patients with MDD, BD, and SZ. We found distinct associations between 3 psychopathological FTD factors (5) and structural connectome measures. On a connectome-wide level, the FTD factor emptiness was negatively associated with the total number of streamlines and mean number of streamlines per edge, while the factor incoherence was negatively associated with the mean number of streamlines in rich club edges. Network-based analyses yielded subnetworks of white matter fiber tracts that were negatively associated with the disorganization and emptiness factors, respectively. These results indicated FTD syndromes to be associated with specific white matter network dysconnectivity. Importantly, subnetwork results did not depend on diagnoses and remained stable after correction for medication and disease severity. Confirmatory analyses of nodes from our identified networks (i.e., cortical brain regions) showed a substantial overlap with brain regions that have been associated with FTD in previous structural MRI studies in SZ (32,33,38).

Based on these findings, 3 new major insights emerge. First, comprehensive post hoc analyses including bootstrapped confidence intervals and Bayesian analysis of covariance on the disorganization and emptiness networks did not reveal any significant diagnosis × FTD factor interaction effects. Our study thus provides evidence for a particular psychopathological syndrome (i.e., disorganization) having a common structural connectome correlate across disorders, which has been hypothesized for a long time (39). While the mean severity of FTD and connectome dysconnectivity may differ between diagnoses (4,45), our findings indicate that the presence of FTD is transdiagnostically correlated with the presence of dysconnectivity in the identified subnetworks, as evidenced by

the spatial overlap of connectome alterations in patients with MDD, BD, and SZ exhibiting FTD. This aligns with studies proposing a (neuro)biological overlap across affective and psychotic disorders in terms of shared genetics, environmental risk factors, cortical measures, and others (1,3,45,65–70). Therefore, this study highlights the need for transdiagnostic, dimensional approaches, which are a key in overcoming the limitations of categorical case-control investigations (3,71,72). This type of approach should aid etiopathogenetic studies across psychiatric disorders (46).

Second, corroborating our findings, our transdiagnostic subnetwork nodes overlapped with GMV regions that have been reported for FTD in patients with SZ (32,33,38). Central hubs (i.e., most connected brain regions within a network) involved in the disorganization subnetwork were the right lingual gyrus, left precuneus, left middle temporal gyrus, left posterior superior temporal sulcus, and right fusiform gyrus, all of which have been associated with FTD in SZ (4,32,33,73) and align in large parts with the language network in the healthy population (74). Moreover, these regions form a known anatomical network by several (long-range) association fibers (75–78). Specifically, the left middle temporal gyrus forms part of the semantic system (79) and is one of the most consistent findings reported in mega- and meta-analyses associated with FTD (32,33,35,80). More generally, it is considered as a core hub of the ventral stream that maps phonological representations onto lexical conceptual representations (81). Central hubs of the emptiness subnetwork were the left precentral gyrus, left insula, left middle temporal gyrus, right superior temporal gyrus, left superior frontal gyrus, and left inferior parietal gyrus. Again, these hubs highly overlap with the anatomical structures that have previously been associated with not only FTD symptomatology in SZ, but also general speech production and processing (4,32,33,82).

Third, the disorganization and emptiness subnetworks differed in their involvement of frontal, temporal, parietal and occipital brain regions and hence in their respective central hubs. This finding indicates a differential representation of FTD symptomatology throughout the brain's connectome. Disorganization FTD symptoms such as tangentiality, circumstantiality, and derailment seem to be correlated with a network of predominantly temporo-parieto-occipital areas, whereas emptiness (i.e., a decrease in the amount of speech, including poverty of speech and content as well as blocking) involves a network of both temporal and frontal structures (4,32,33,38,82,83).

Finally, the central hubs in both subnetworks were predominantly located in the left hemisphere. However, hubs of the right hemisphere were also involved, thus excluding a purely left hemispheric involvement in FTD (84).

## Limitations

Some limitations can be noted. First, the cross-sectional nature of this study prohibits implications about causality or directionality. Second, while we conducted comprehensive post hoc analyses to examine the evidence for diagnosis × FTD interaction effects, it is important to acknowledge that the higher proportion of participants diagnosed with MDD compared with participants diagnosed with BD and SZ could have influenced these results. Therefore, it is possible that slightly different results could have been obtained in a sample with a more balanced ratio of diagnostic groups. Third, although results remained stable after correction for current medication, we could not account for lifetime cumulative intake of psychotropic medication; nevertheless, disease severity would correlate with lifetime cumulative doses, which did not explain our FTD results.

## Conclusions

This study shows evidence of a transdiagnostic psychopathological syndrome correlation with global and local structural connectome measures. Subnetworks of the structural connectome were independent of diagnosis, medication, and disease severity. This maps on the old dysconnectivity hypothesis of patients with SZ in general and their speech impairments in particular. Finally, our results particularly highlight the importance of transdiagnostic, dimensional studies in psychiatric research.

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