

Dimensions of Formal Thought Disorder and Their Relation to Gray- and White Matter Brain Structure in Affective and Psychotic Disorders

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Factorial dimensions and neurobiological underpinnings of formal thought disorders (FTD) have been extensively investigated in schizophrenia spectrum disorders (SSD). However, FTD are also highly prevalent in other disorders. Still, there is a lack of knowledge about transdiagnostic, structural brain correlates of FTD. In $N = 1071$ patients suffering from DSM-IV major depressive disorder, bipolar disorder, or SSD, we calculated a psychopathological factor model of FTD based on the SAPS and SANS scales. We tested the association of FTD dimensions with 3 T MRI measured gray matter volume (GMV) and white matter fractional anisotropy (FA) using regression and interaction models in SPM12. We performed post hoc confirmatory analyses in diagnostically equally distributed, age- and sex-matched sub-samples to test whether results were driven by diagnostic categories. Cross-validation (explorative and confirmatory) factor analyses revealed three psychopathological FTD factors: disorganization, emptiness, and incoherence. Disorganization was negatively correlated with a GMV cluster comprising parts of the middle occipital and angular gyri and positively with FA in the right posterior cingulum bundle and inferior longitudinal fascicle. Emptiness was negatively associated with left hippocampus and thalamus GMV. Incoherence was negatively associated with FA in bilateral anterior thalamic radiation, and positively with the hippocampal part of the right cingulum bundle. None of the gray or white matter associations interacted with diagnosis. Our results provide a refined mapping of cross-disorder FTD phenotype dimensions. For the first

time, we demonstrated that their neuroanatomical signatures are associated with language-related gray and white matter structures independent of diagnosis.

Key words: gray-matter-volume/fractional anisotropy/dimensional/factor analysis/neuroimaging

Introduction

Formal thought disorder (FTD) refers to a construct measuring deviant thinking, speech, and communication.¹ FTD has been extensively investigated in schizophrenia (SZ), and schizoaffective disorder (SZA) (henceforth referred to as schizophrenia spectrum disorders, SSD), but much less in bipolar disorder (BD) and major depressive disorder (MDD) (all together henceforth referred to as major psychiatric disorders).^{1,2} Prevalence rates of FTD range from 53% in MDD up to 80% in SZ.¹ Patients with FTD have a higher risk for inpatient treatment, and they stay significantly longer in hospital.³

To provide significant progress for our understanding of FTD as a core psychiatric syndrome, both, phenotypes and brain correlates, must be untangled across diagnoses. This transdiagnostic endeavor is further driven by results showing large overlaps across MDD, BD, and SSD not only in symptomatology, but also in molecular genetic^{4,5} and early environmental risk.⁶ Besides, it has long been hypothesized, but not yet scientifically confirmed, that a particular psychopathological symptom/syndrome (e.g.

disorganization) has a common brain structural correlate across psychiatric disorders.⁷

Factor analyses of FTD symptomatology were previously performed in SZ patients. Only few studies investigated FTD dimensions across diagnosis, showing common psychopathological dimensions.^{2,8–10} Depending on the scale and population, FTD can be broken down into one to six factors.^{2,11–13} Meta analyses^{13,14} revealed two factors (i.e. positive and negative FTD). While there is consensus about one negative/poverty domain,¹⁵ positive FTD (pFTD) has been divided into two (disorganization, verbosity) up to five (disorganization, idiosyncratic, semantic, attentional, referential) factors in SZ patients.^{12,13} pFTD symptoms are best represented by an increased amount of speech, tangentiality, derailment, and circumstantiality.¹ Negative FTD (nFTD) usually comprise a quantitative deficit resulting in poverty of speech, blocking, and increased latency.²

Language production and processing is constituted by distributed cortical and subcortical networks.¹⁶ Altered brain structure in these language circuits might result in FTD. Diagnostically independent brain structural correlates of FTD symptoms would completely open up new approaches for pathogenic and etiological research. Similar to FTD symptomatology, the neuroanatomical correlates of FTD have mainly been examined in SZ patients, but not in other diagnoses. Studies in SZ patients have shown that positive/disorganized FTD correlated negatively with the gray matter volumes (GMV) of the bilateral middle and superior temporal gyri, inferior frontal gyri, the middle, medial and superior frontal gyri, the left amygdala-hippocampus complex, the precuneus, the planum temporale, and the insula.^{17–19} nFTD have been negatively associated with GMV in the bilateral insula, the precuneus, the amygdala, the anterior and posterior cingulate gyri, and the medial frontal/orbitofrontal cortices.^{18,20} GMV associations with FTD across the major psychiatric disorders remain largely elusive.

The association of FTD dimensions and white matter diffusion tensor imaging (DTI) has been investigated to a much lesser extent than GMV in SZ and not at all in other diagnoses. Specifically, in SZ patients, a general dysconnectivity has been proposed.²¹ Moreover, one study indicated a structural language dysconnectivity in the semantic network which may be linked to FTD.²² Previously, a number of fiber tracts has been associated with FTD (eg, inferior longitudinal fascicle (ILF), left uncinate fascicle,²³ superior longitudinal fascicle,²³ inferior fronto-occipital fascicle,²⁴ cingulum bundle (CB),^{25,26} anterior thalamic radiation (ATR)).^{24,26} However, there are no studies investigating white matter associations of FTD across the major psychiatric disorders, although FTD is common in all.

We used a cross-validation approach to disentangle the psychopathological factor structure of FTD in MDD, BD, and SSD. We associated the psychopathological factors with gray and white matter in $N = 1071$. Based on previous findings,²⁷ we hypothesized a factor model including

one negative/emptiness factor, and additional positive domains. Moreover, we hypothesized that the gray and white matter alterations previously associated with FTD in SZ are present in patients, independent of diagnosis.

Methods

Participants

As part of the FOR2107 cohort,²⁸ a broad spectrum from acutely ill to remitted in- and outpatients from the departments of psychiatry, university hospitals in Marburg and Münster, Germany and other psychiatric hospitals in their vicinity, were included in the study. All procedures were approved by the local Ethics Committees according to the Declaration of Helsinki and patients gave written informed consent to the study protocol.

We excluded patients with $\text{IQ} < 80$, history of head trauma or unconsciousness, current intake of benzodiazepines, and neurological illness (all assessed during the semi-structured interview and via self-reporting questionnaires) from the present study. After quality checks of the T1 weighted scans and exclusion of patients with incomplete data, we analyzed 1071 patients (aged 18–65) who met the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) for MDD, BD, and SSD (SZA $n = 42$, SZ $n = 75$) (see table 1). For the DTI analyses, we excluded additional $n = 241$ patients due to artifacts (eg, caliber gaps) ($n = 79$), poor data quality due to wrong positioning ($n = 21$), and nonavailable DTI data at the time of analysis ($n = 141$) leaving a DTI sample of $n = 830$ (supplementary table 3)

Psychopathology Assessment

FTD symptoms were assessed during a clinical interview including the Structured Clinical Interview for DSM-IV (SCID-I) and psychopathology scales. Ratings were conducted during or immediately after the interview. Acute positive and negative symptoms were assessed with the scale for the assessment of positive symptoms (SAPS)²⁹ and the scale for the assessment of negative symptoms (SANS).³⁰ Interrater reliability was assessed with the interclass coefficient, achieving good reliability of $r > .86$ in both scales. For the present analysis, we used the items of the alogia subscale of the SANS (poverty of speech, poverty of content, blocking, increased latency of response), and the pFTD subscale items of the SAPS (derailment, tangentiality, incoherence, illogicality, circumstantiality, pressure of speech, distractibility, clanging).

FTD Psychopathology Factor Analyses

We investigated the factorial structure of FTD symptoms. To cross-validate FTD factorial dimensions in two subsamples, we divided the total sample of $N = 1071$ using

Table 1. Descriptive statistics of the psychopathological factor analysis and voxel-based morphometry sample ($N = 1071$)

	Major depressive disorder ($n = 821$)	Bipolar disorder ($n = 133$)	Schizophrenia spectrum disorders ($n = 117$)	<i>P</i>
Age	36.67 (13.19)	41.34 (11.93)	38.23 (11.72)	<.001 ^a
TIV	1561.53 (152.8)	1578.32 (144.88)	1578.83 (183.53)	.303
Years of education	13.21 (2.74)	14.06 (2.78)	12.52 (2.68)	<.001 ^b
SANS alogia subscale	0.49 (1.31)	0.62 (1.37)	1.83 (2.64)	<.001 ^c
SAPS pFTD subscale	0.36 (1.4)	1.71 (3.21)	3.13 (4.47)	<.001 ^d
SANS sum	7.47 (8.65)	5.74 (7.33)	13.57 (12.4)	<.001 ^c
SAPS sum	0.66 (2.08)	2.37 (4.3)	10.03 (12.52)	<.001 ^d
YMRS sum	1.43 (2.1)	3.89 (5.92)	2.69 (4.94)	<.001 ^c
HAM-D sum	8.38 (6.4)	6.78 (5.82)	6.74 (5.79)	.002 ^e

Note: Mean (standard deviation); TIV: total intracranial volume; SANS: scale for the assessment of negative symptoms³⁰; SAPS: scale for the assessment of positive symptoms²⁹; YMRS: Young mania rating scale⁷⁹; HAM-D: Hamilton rating scale for depression⁸⁰. Tukey's post hoc test was performed to investigate group differences.

^aMDD < BD.

^bMDD < BD; SSD < BD.

^cMDD < SSD; BD < SSD.

^dMDD < BD, SSD; BD < SSD.

^eSSD < MDD; BD < MDD.

the “mindiff” package³¹ in R (version 4.0.4).³² To provide a comparable distribution of diagnostic categories in both samples, we randomly split each diagnostic group separately accounting for age and sex as covariates, resulting in the explorative psychopathology sub-sample 1 with $n = 537$ (supplementary table 1) and the confirmatory psychopathology sub-sample 2 with $n = 534$ (supplementary table 2).

The explorative factorial structure of FTD was investigated using a principal axis factor analysis (PFA) with promax (oblique) rotation of sub-sample 1 (*Statistical Package for Social Science*, IBM, version 25). Due to interpretability, items with factor loadings <0.5 were not considered in the analysis.¹⁰ Cronbach's alpha coefficients³³ were used to test the internal consistency.

Validating the explorative model, we performed a confirmatory factor analysis (CFA) using *Mplus* (version 8.4)³⁴ in sub-sample 2. Additionally, we tested the confirmatory model for the whole sample ($N = 1071$). Comparable to the approach performed by Roche et al.,¹³ we tested confirmatory factor models with less than three factors and several factor models derived from previous studies^{12,13,35–37} to investigate if they would have a superior fit than our model.

To rule out potential effects caused by the unequal distribution of DSM-IV diagnostic categories, we tested the model again in a smaller subsample with the same number of patients from each diagnosis, matched for age-and sex (supplementary tables 4 and 5). Matching of the subsamples was performed using the “MatchIt” package³⁸ in R.³² We used the maximum-likelihood-method (MLM) to estimate confirmatory models since this estimator is robust to standard errors and is one of the most common estimators.³⁹ Goodness of fit was measured with chi-square significance test, comparative

fit index (CFI),⁴⁰ and root mean square error of approximation (RMSEA).⁴¹ We extracted latent standardized factor scores for each patient.

MRI Data Acquisition and Preprocessing

T1 weighted images and diffusion-weighted images were obtained using a 3 T MRI scanner (Münster: Prisma, Siemens, Erlangen, Germany; Marburg: Tim Trio, Siemens, Erlangen, Germany). In Münster, a 20 channel and in Marburg a 12 channel head matrix Rx-coil were used. MRI data were acquired according to an extensive quality assurance protocol.⁴²

T1 weighted images were acquired using a fast gradient-echo MP-RAGE sequence with a slice thickness of 1.0 mm consisting of 176 sagittal orientated slices in Marburg and 192 slices in Münster and a FOV of 256 mm and the following parameters at the two sites: Marburg: TR = 1.9 s, TE = 2.26 ms, TI = 900 ms, flip angle = 9°; Münster: TR = 2.13 s, TE = 2.28 ms, TI = 900 ms, flip angle = 8°.

DTI scans were acquired using an epi2d sequence (TR 7300 ms, TE 90 ms, FOV 320 mm, phase encoding anterior-posterior, 56 slices with 2.5 mm slice thickness in Münster, 3 mm thickness in Marburg) with a final voxel resolution of $2.5 \times 2.5 \times 2.5 \text{ mm}^3$. For all patients, two sets of 30 diffusion-weighted images ($b = 1000 \text{ s/mm}^2$) and four nondiffusion weighted images ($b = 0 \text{ s/mm}^2$) were acquired. MRI data acquisition and the assessment of FTD symptoms were performed within the same week.

For T1 weighted images, we used the default parameters as implemented in the CAT12 toolbox (Computation Anatomy Toolbox for SPM, build 1184, Christian Gaser, Structural Brain Mapping group, Jena University Hospital, Germany) building on SPM12 (Statistical Parametric Mapping, Institute of Neurology, London, UK). During

pre-processing, images were spatially registered, segmented,^{43,44} and normalized.⁴⁵ T1-MRI data sets were spatially smoothed with a Gaussian kernel of 8 mm FWHM. Total intracranial volume (TIV) was calculated during pre-processing.

Before pre-processing, all DTI scans were visually inspected for major artifacts or caliber gaps. For DTI analyses, we used a tract-based spatial statistics (TBSS) approach running under FSL (version 6.0; the Oxford Centre Functional Magnetic Imaging Software Library; Oxford, UK⁴⁶). Data were pre-processed using default parameters. During pre-processing, data were corrected for motion and Eddy-Current artifacts.⁴⁷ Images were nonlinearly registered into standard Montreal Neurological Institute (MNI) space⁴⁸ using a FSL template. Finally, fractional anisotropy (FA) maps were projected on mean skeletons with a 0.2 threshold to prevent alignment errors.

Voxel-Based Morphometry and Diffusion-Tensor-Imaging Statistical Analyses

Brain structural analyses were performed using separate linear regression analyses for each factor. MRI data acquisition was performed according to a comprehensive quality protocol. Several nuisance variables of no interest were included: age, sex, and total intracranial volume. In addition, as recommended by the MRI quality assurance protocol of the FOR2107 cohort two dummy-coded variables accounting for the change of a body coil and the site (Marburg pre body coil: yes/no, Marburg post body coil: yes/no with Münster as reference category, change of gradient coil were entered to the models.^{28,42} Considering potential medication effects, three dummy-coded covariates (yes/no) accounting the current intake of antidepressants, mood stabilizers, and antipsychotics were entered into the statistical models. To further exclude potential medication effects, eigenvariates of significant clusters were correlated with the current chlorpromazine equivalents and the Sackheim score (antidepressant medication).⁴⁹

VBM analyses were performed using SPM12 (v6906). As recommended for VBM analyses, absolute threshold masking with a threshold value of 0.1 was used (<http://dbm.neuro.uni-jena.de/cat/>). Results were considered significant at $P < .05$ cluster-level family-wise-error-corrected (FWE) for multiple comparisons after an initial threshold of $P < .001$ uncorrected, and a $k > 10$ threshold. Cluster labeling was applied using the Dartel space Neuromorphometrics atlas.

Tract-based, voxel-wise DTI analyses were performed using threshold-free cluster enhancement (TFCE). We performed 5000 permutations for GLM contrast generation.⁵⁰ The JHU DTI 81 white-matter labels atlas and the JHU white-matter-tractography atlas⁵¹ were used for cluster labeling. MNI coordinates were retrieved with the cluster tool of FSL. Results were considered significant at $P < .05$ FWE-corrected, and threshold $k > 10$.

ANCOVA interaction analyses for each factor with DSM-IV diagnostic categories were performed in SPM and FSL (factor x diagnosis, full-factorial model), to test whether transdiagnostic brain correlates of FTD dimensions were driven by DSM-IV diagnostic categories. Adding DSM-IV diagnostic categories as covariates to the multiple regression analyses would have contradicted our approach as diagnoses somehow rest on symptoms.

Since DSM-IV categories were unequally distributed, we again performed multiple regression analyses as described above in a sub-sample with equal patient numbers for each of the three diagnoses ($n = 351$ for the VBM sample and $n = 309$ for the DTI sample). Therefore, we used significant clusters from the total sample analyses as ROIs for the analyses in the matched sample. ANCOVA interaction analyses in SPM and FSL were performed in the matched sample, too.

To better understand brain structural mechanisms across white and gray matter, we tested whether the VBM and DTI clusters correlating with one of the factors were associated, using partial correlations including the covariates from brain structural analysis. Hereof, eigenvariate values approximating mean volume/FA of significant clusters were extracted.

Results

Exploratory Psychopathology Factor Analysis of Subsample 1

PFA revealed a 3-factor structure (table 2, supplementary figure 1). In factor models with more than three factors the last factor comprised only one symptom (SAPS32: distractibility). Factors only including one item cannot be considered as a symptom dimension. The 3-factor model included (explaining 50.58% of variance): disorganization ($\alpha = .857$; 21.76 % of variance), emptiness ($\alpha = .757$; 15.23% of variance), and incoherence ($\alpha = .728$; 13.58% of variance).

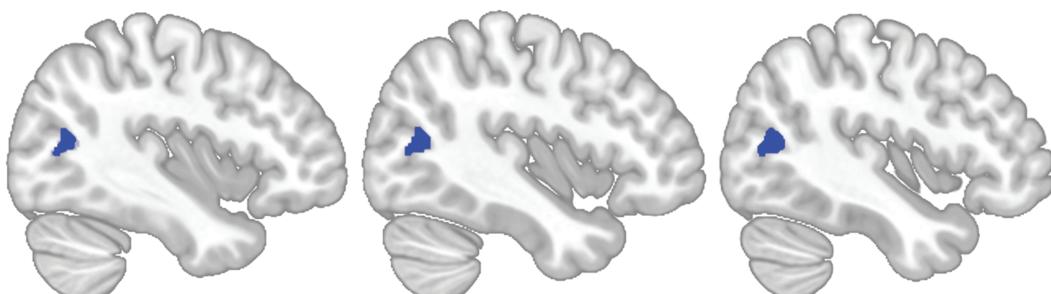
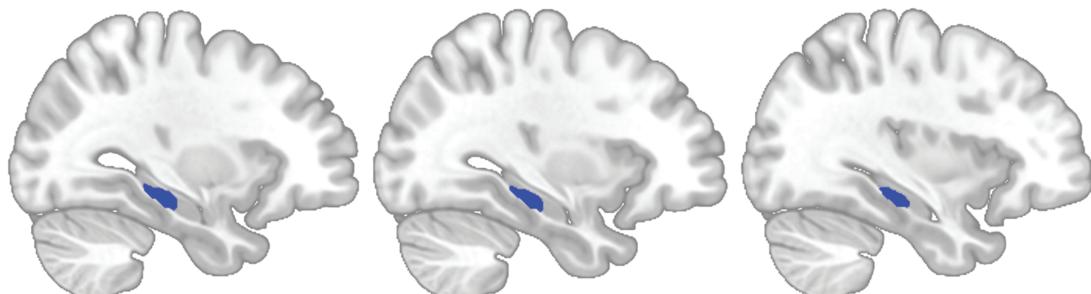
Confirmatory Psychopathology Factor Analysis of Subsample 2

Cross-validating the explorative model, we performed a confirmatory factor analyses using the second sample ($n = 534$). We confirmed the 3-factor model. Fit indices of the second sample showed an acceptable fit: $\chi^2 = 44.88$, $df = 21$, $P < .0001$, $CFI = 0.909$, $RMSEA = 0.046$. To test whether our model fit the whole sample, we performed a confirmatory factor analysis in the whole sample ($N = 1071$), showing a good fit: $\chi^2 = 66.097$, $df = 21$, $P < .0001$, $CFI = 0.928$, $RMSEA = 0.045$. We were able to replicate the model in the age- and sex-matched sample, too (supplementary results 1).

We tested if explorative models with one or two factors have a superior fit than the three-factor model, showing that the three-factor model had a considerably better fit. Moreover, factor solutions from previous studies were

Table 2. Explorative psychopathological FTD factors of sample 1 ($n = 537$)

Factor	Item	Symptom	Loading	Cronbach's alpha
Disorganization	SAPS 27	Tangentiality	0.917	0.857
	SAPS 30	Circumstantiality	0.768	
	SAPS 26	Derailment	0.754	
	SAPS 31	Pressure of speech	0.680	
Emptiness	SANS 8	Poverty of speech	0.741	0.757
	SANS 9	Poverty of content	0.722	
	SANS 11	Increased latency of response	0.656	
	SANS 10	Blocking	0.556	
Incoherence	SAPS 28	Incoherence	0.892	0.728
	SAPS 29	Illogicality	0.672	
	SAPS 32	Distractibility	0.546	

A Association of disorganization and gray matter volume**B Association of emptiness and gray matter volume****Fig. 1.** A and B: Negative association of formal thought disorder dimensions and gray matter volume in patients with major depressive disorder, bipolar disorder, and schizophrenia spectrum disorder ($N = 1071$). Clusters are shown at $P < .05$, family wise error-corrected (initial cluster-defining threshold of $P < .001$).

tested.^{12,13,35–37} Results indicated that our three-factor model showed superior fit compared to published models (supplementary table 6). Therefore our model was chosen for further brain structural analyses.

Association of FTD Psychopathology Factors With Gray Matter Volume

Next, we investigated the association of each FTD factor and GMV in the whole sample ($N = 1071$). Disorganization correlated negatively with the left (L) middle occipital gyrus (MOG) (63%), L inferior occipital gyrus (29%), and the L angular gyrus (7%) ($k = 872$, $x/y/z = -40.5/-66/12$, $t = 4.7$,

$P = .035$ FWE) (figure 1A). Emptiness showed a negative correlation with the L hippocampus (41%), L thalamus proper (7%), L parahippocampal gyrus (7%), and the L posterior cingulate gyrus (5%) ($k = 842$, $x/y/z = -31.5/-25.5/-15$, $t = 4.19$, $P = .039$ FWE) (figure 1B). There was no FWE corrected association for the incoherence factor. Full-factorial interaction analyses (diagnostic category x FTD factor) were performed to test if local GMV associations with FTD dimensions were driven by DSM-IV diagnoses. There was no interaction effect in the total sample ($N = 1071$).

To further test if GMV associations were driven by DSM-IV diagnoses, we performed regression analyses

again in an age- and sex-matched sample which included the same number of patients from each of the three diagnostic categories. Significant clusters from the whole-brain analysis in total sample could be replicated in the diagnostically matched sample ([supplementary results 2](#)). Additionally, there was no interaction with DSM-IV diagnoses for both the disorganization and the emptiness factor on GMV in the diagnostically matched sample, either. Significant GMV associations were not correlated to chlorpromazine equivalents nor to the Sackeim score.

Association of FTD Factors and FA

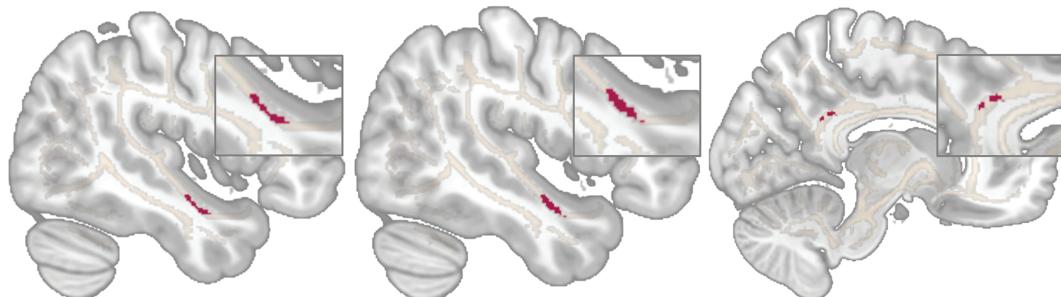
We tested the relationship of FTD factors and the microstructure of white matter using multiple regression analyses ([figure 2A and B, table 3](#)). Disorganization and incoherence were differentially associated with FA,

including positive associations of disorganization with the R ILF and posterior cingulum bundle. Incoherence was negatively correlated with the bilateral ATR and positively with the hippocampal part of the cingulum bundle. There was no association with the emptiness factor. We retrieved significant clusters of the total sample in the age- and sex-matched, too ([supplementary table 7](#)). There was no interaction effect (diagnosis x FTD factor) in the total and in the matched sample. Significant FA tracts were not correlated to chlorpromazine equivalents nor to the Sackeim score.

Association of Significant GMV and DTI Clusters

As we detected alterations in both brain modalities for the disorganization factor, we investigated the correlation between these results to better understand brain

A Association of disorganization and fractional anisotropy



B Association of incoherence and fractional anisotropy

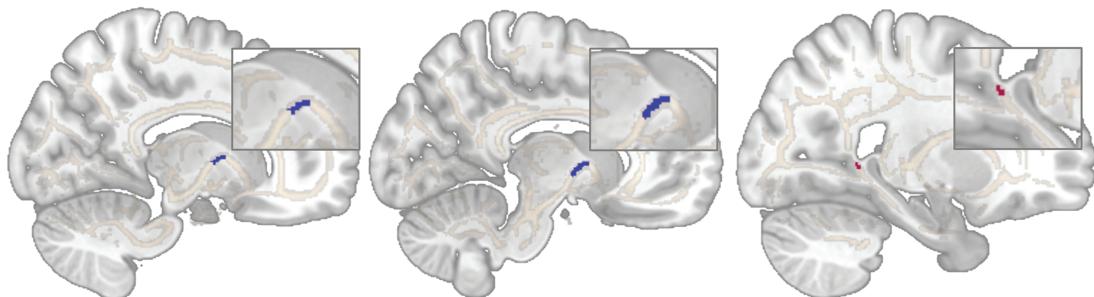


Fig. 2. A and B: Association of formal thought disorder dimensions and fractional anisotropy in the DTI sample ($n = 830$). Clusters are shown at $P < .05$, family-wise-error-corrected. Clippings show an enlargement of the clusters.

Table 3. Association of formal thought disorder factors and fractional anisotropy diffusion tensor imaging tracts ($n = 830$)

Factor	Corre-lation	Coordinates of the maximum intensity voxel (x/y/z) MNI	Anatomical labelling	Hemi-sphere	k	P
disorgani-zation	positive	11/-48/26	posterior cingulum inferior longitudinal fasciculus	R	14	.036
	positive	46/-7/-16			60	.038
incoherence	negative	-12/2/4	anterior thalamic radiation anterior thalamic radiation cingulum/ hippocampus	L R R	201	.02
	negative	14/1/6			157	.012
	positive	23/-44/2			24	.028

Note: R: right, L: left

structural mechanisms. Therefore, we used partial correlation analyses for the disorganization FTD dimension in the whole sample and correlated GMV clusters with FA white matter tracts. There was no correlation between VBM and DTI clusters.

Discussion

To overcome the shortcomings of categorical approaches,^{52–56} we investigated the association of dimensional FTD psychopathological factors with white and gray matter in a large transdiagnostic cohort of patients with MDD, BD, and SSD. Our study revealed an exploratory and confirmatory psychopathological three-factor model across disorders comprising disorganization, incoherence, and emptiness. Disorganization was negatively associated with a GMV cluster comprising parts of the temporo-occipital language junction. Furthermore, we found a positive fiber tract association of disorganization with the R posterior CB and the R ILF. Incoherence was negatively associated with the bilateral ATR, and positively with the R cingulum/hippocampus bundle. Emptiness was negatively associated with a GMV cluster comprising the L hippocampus and thalamus. Importantly, all VBM and DTI FTD factor associations were independent of DSM-IV diagnoses. This points to a shared relationship between FTD and brain structure across diagnoses. The present study provided evidence for the feasibility of dimensional approaches by establishing a transdiagnostic factor model and by linking psychopathological factors to brain structural measures across disorders. Results endorsed the hypothesis of particular symptom complexes (i.e. syndromes/factors) sharing common (neuro-) biological mechanisms independent of DSM diagnostic categories.^{52,57–59} There was no correlation between VBM and DTI clusters of disorganization indicating one FTD syndrome/dimension can arise from different brain structural changes, a result well known from aphasia research.

Previous studies that only included patients with SZ mainly identified models with two to four psychopathological factors.^{1,12,13} General psychopathology in SZ has been divided into four factors. Two of them (positive and negative) remained longitudinally stable and could be related to functional connectivity profiles of the ventro-medial frontal cortex, temporo-parietal junction, and the precuneus.⁶⁰ We fundamentally extend psychopathological factor models of FTD across a range of psychotic and affective disorders using a cross-validated model and identified three factors. The factorial model of FTD in the present study reflects the distinction of FTD into quantitative and qualitative domains, which has also been proposed by other groups such as SyNoPsis.^{53,61} In line with previous studies,^{2,62} we were able to show large psychopathological overlapping across disorders, resulting in a model of FTD common to the three diagnoses.

Pressure of speech loaded on the disorganization factor, which might reflect the blurring of different diagnostic categories.³ Differences between our and previous models in SZ might be due to methodological aspects (e.g. scale, population, extraction method). Compared to other published models on FTD dimensions,¹³ ours had superior goodness of fit.

Our study provides for the first time large-scale evidence that FTD dimensions are differentially correlated with gray and white matter anatomical structures across diagnoses. Disorganization was negatively associated with a GMV cluster in the L temporo-occipital language junction comprising parts of the angular and middle occipital gyri. The L angular gyrus is part of the Wernicke speech area which has been associated with the total severity of FTD symptoms in SZ patients,⁶³ corroborating our results. Supporting the results of the present study, this anatomical structure has been reported as part of the semantic network in SZ patients, which is also associated with the severity of FTD symptoms.²² Moreover, the L MOG has been linked to semantic paraphasia and neologisms during free speech production in aphasia patients,⁶⁴ pointing to derailed speech which coincides with disorganization across psychiatric patients in the present study. Disorganization was further positively correlated with FA of two white matter tracts: the R ILF and the R posterior CB. The ILF indirectly connects posterior temporal and occipital areas and the frontal lobe.⁶⁵ Together with other ventral white matter tracts, the ILF forms part of the semantic ventral stream,⁶⁶ which is implicated in linking objects to the appropriate lexical meaning⁶⁷ and more generally in lexical access. The right lateralization might indicate a reversed lateralization in patients, which has also been observed during fMRI speech production tasks in SZ.⁶⁸ These associations might indicate a global brain structural dysconnectivity which has already been reported in SZ patients,²¹ being generally implicated in FTD.^{22,69}

Incoherence was correlated with white matter tracts in the bilateral ATR and the R cingulum-hippocampus bundle. The ATR connects the dorsolateral prefrontal cortex with the thalamus.⁷⁰ Altered FA in the ATR has been reported in BD⁷⁰ and SZ⁷¹ patients. Our results further coincide with a previous SZ study²⁴ showing bilateral associations of the ATR with a global FTD language score. Further evidence is given by lesion studies in aphasia patients²⁶ indicating that the reduced FA of the ATR is associated with impairments in verbal fluency tasks. There was no association of incoherence and GMV, indicating differential brain structural mechanisms being involved in different FTD domains.

Complementary to a study⁷² investigating limbic links to paranoia using resting-state functional connectivity, emptiness was negatively associated with a GMV cluster comprising parts of the L hippocampus, thalamus, and posterior cingulate gyrus. This result is in line with

previous studies in SZ patients.^{17,18,20} Additionally, functional imaging studies in SZ indicated that impaired free word generation is mediated by the hippocampus.^{73,74} No correlations to white matter FA were present.

Finally, the results of the present study support the hypothesis⁵³ of FTD dimensions being linked to language-related anatomical structures independent of categorical diagnosis. In contrast to previous studies investigating neural correlates of FTD both on a structural as well as functional level, we did not identify associations between FTD dimensions and the left superior and middle temporal gyri, which have previously been reported as core regions implicated in FTD.^{17,18,75,76} This finding might point to a diagnosis-specific (ie, SZ) association between FTD and the middle and superior temporal gyri.

Limitations

Some limitations have to be noted. First, the MDD group was the largest in our transdiagnostic sample. However, interaction analyses in both the whole and the diagnostically matched sample revealed no interaction of diagnostic categories and FTD factors on local brain structural correlates. Second, SANS and SAPS are designed to measure a broad variety of symptoms, rather than specifically FTD.^{2,77} Using more detailed scales collecting even more FTD symptoms might result in a higher number of extracted factors and subsequently in differential brain structural correlates of FTD. Nevertheless, SANS and SAPS are two economical and well-validated scales that have been widely used in FTD research. Third, factor dimensions were based on current FTD symptoms and statistical models did not include remission of patients. Correlating state measures with brain structure might lead to volatile results.⁷⁸ Nevertheless, acute syndromes may be an indication for a particular neuroanatomical, state-independent alteration that outlasts current symptoms. Fourth, current intake of three medication classes (antipsychotics, antidepressants, mood stabilizers) was entered as dichotomous variables into the statistical models. This method does not account for current doses nor for lifetime cumulative intake of psychotropic medication, which might have influenced results. Fifth, since this is a cross-sectional study, no implications can be drawn about causality or directionality, which might be relevant for somewhat different trajectories of brain volume loss over time across diagnoses. However, this is an unresolved matter.

Conclusion

Our results provide first evidence of common neurobiological structures involved in FTD across affective and psychotic disorders, independent of diagnosis. Since the anatomical correlates of white and gray matter did not correlate with each other, we speculate that firstly, the same psychopathological symptoms can result from

changes in different neuroanatomical substrates, a fact known from aphasia research, which might explain in part the heterogeneous findings of FTD neural correlates in SZ. Secondly, these different neuroanatomical correlates might be due to a diverse range of environmental and genetic factors (and their interactions) impacting at different time points the developing brain. Consequently, different etiologies may result in a range of diverse brain changes, nevertheless giving rise to a homogeneous syndrome, e.g. disorganization or incoherence.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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