

# Formal thought disorder is associated with brain network changes across diagnoses

*A new study provides evidence for a long-discussed hypothesis: For the first time, researchers were able to show that alterations in the structural networks of affective and psychotic disorder patients' brains correlate with the patients' symptoms and not with their diagnosis. This study thus highlights the need for transdiagnostic, syndromal approaches to mental disorders.*

By Stefanie Flunkert

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**New Ground article reviewed by:** Frederike Stein and Tilo Kircher

## Formal thought disorder and categorization of symptoms

Formal thought disorder (FTD) is a phenomenologically defined syndrome with a complex of symptoms traditionally linked to schizophrenia and which can also be observed in other psychiatric disorders such as major depressive, bipolar, and schizoaffective disorders, and – to a much lesser extent – also in healthy people. So far, however, no studies have investigated associations between FTD and alterations in global macroscopic brain networks, even though dysconnectivity between brain areas has long been suspected of being related to psychiatric disorders in general and FTD in particular.

Now, a team of researchers led by Tilo Kircher and Jonathan Repple has demonstrated that dysconnectivity of white matter subnetworks is relevant for FTD symptoms in patients diagnosed with a variety of psychiatric disorders, and not only those with schizophrenia, as previously believed. More specifically, they studied how various cortical brain regions are interconnected by axonal fiber tracts – bundles of nerve fibers that constitute the essential core of the brain's white matter – and showed how connectivity is associated with specific FTD symptoms in a large group of patients with depression, bipolar disorder, and schizophrenia.

The results of this study highlight the need for transdiagnostic, symptom-based rather than diagnosis-based approaches and could potentially change the way psychiatric disorders are categorized. Although more research is needed, patients could ultimately benefit from treatment approaches based on underlying changes in brain networks rather than their diagnosis.

Depending on the diagnosis and the stage of illness, FTD symptoms vary greatly in their intensity, but are primarily linked to speech and cognition. So-called positive formal thought disorder symptoms include derailment and loosening of associations, an increased amount of produced speech such as logorrhea or pressured speech, the use of neologisms, and stilted speech phenomena such as manneristic speech. Negative FTD symptoms can be summarized as a deficit in speech quantity and thought production such as poverty of speech and content, slowed thinking, and blocking.

### **New categorization of FTD symptoms into psychopathological dimensions**

Based on their previous study on structural brain correlates of FTD, published in 2022 in the *Schizophrenia Bulletin* (see here: <https://doi.org/10.1093/schbul/sbac002>), the authors group FTD symptoms into three psychopathological dimensions: disorganization, emptiness, and incoherence. The FTD dimension disorganization includes the symptoms tangentiality, circumstantiality, derailment, and pressure of speech, while the dimension emptiness includes poverty of speech and content, increased latency of response, and blocking. The third dimension, incoherence, includes symptoms such as incoherence, illogicality, and distractibility.

Using magnetic resonance imaging (MRI), the team that conducted the 2022 study measured gray matter volume and white matter fractional anisotropy – the latter being a measure of fiber tract density – and correlated the three dimensions to specific gray and white matter structures, mostly in language-related brain areas. Since their findings proved to be dimension-specific while independent of the respective diagnosis, they are applicable across the three disorders major depression, bipolar disorder and schizophrenia.

### **Associating FTD symptoms with alterations in brain structural networks**

In their new *Biological Psychiatry* publication, Tilo Kircher and lead authors Frederike Stein and Marius Gruber went one step further: “Brain structural network connectivity of formal thought disorder dimensions in affective and psychotic disorders” builds on the hypothesis that particular FTD symptoms are associated with specific alterations in brain structural networks across diagnoses. These networks are further postulated to include brain regions that are already known to be associated with FTD in schizophrenia. For their study, the authors drew on a subgroup of 864 participants who had already been evaluated in their 2022 work. All participants were diagnosed with major depressive disorder, bipolar disorder, or schizophrenia, based on the diagnostic and statistical manual of mental disorders (DSM-IV-TR). To evaluate the participants for FTD symptoms, the authors used the Scales for the Assessment of Positive Symptoms (SAPS) and Negative Symptoms (SANS).

### **Diffusion-weighted MRI analyses in vivo**

Each participant’s head was scanned using contrast-enhancing T1 MRI as well as diffusion-weighted magnetic resonance imaging (diffusion MRI) to reconstruct the brain’s structural connectome, which produced a comprehensive map of axonal fiber tracts that connect functionally specialized brain regions. The diffusion MRI signal makes it possible to track fiber tracts, yielding insights into existing connections between brain regions and thus the network, including smaller subnetworks, of the brain.

## Measuring brain structural connectivity

In the next step, the authors used the MRI images to reconstruct the strength of white matter connectivity between 114 cortical gray matter brain regions. Each participant's anatomical connectome was stored in a connectivity matrix where rows and columns represented the brain regions, considered to be network nodes, while matrix entries represented the strength of the network's edges as constituted by the white matter fiber tracts connecting these regions, with a zero indicating no connection.

The connectivity strength between nodes was further evaluated by calculating the number of streamlines present in the respective edges. Streamlines can be understood as virtual entities representing physical axon connections. To mathematically construct them, sets of local fiber tract orientations are considered as three-dimensional vector fields and global fiber trajectories as their streamlines. Streamlines are thus curves that run at a tangent to the vector field and can be represented in three-dimensional space. The existence of an edge was assumed if it comprised at least three reconstructed streamlines.

However, deriving streamlines from the MRI images – in which one volume pixel can contain several hundreds of thousands of fiber tracts and their orientations – required extensive modeling and computing.

Based on their analyses, the authors calculated three parameters to evaluate the global connectivity strength of each participant's connectome: the number of edges in the connectivity matrix, the total number of streamlines within their connectome, and the mean number of streamlines per edge.

To assess whether FTD is linked to changes across all hierarchical levels of the connectome, nodes were categorized into hierarchical classes: Hierarchically higher nodes include brain regions with numerous axonal fiber tract connections, so-called hub nodes, while hierarchically lower nodes include brain regions with only a few axonal fiber tract connections, so-called non-hub nodes. To define hierarchical classes, the authors used the rich club organization of networks method. Lastly, they used network-based statistic (NBS) to analyze network-level effects.

## Associations between FTD and structural connectivity

Linear regression of these parameters with the three dimensions disorganization, emptiness and incoherence revealed negative associations between these factors, i.e., a lower connectivity corresponded to a higher score in specific dimensions. In detail, a low total number of streamlines within each patient's connectome, as well as a low mean number of streamlines per edge, was associated with a high score in the dimension emptiness. Furthermore, a low mean number of streamlines per edge that connect hub regions was associated with a high score in the dimension incoherence. Several subnetworks of edges were further identified to be negatively associated with the FTD dimensions disorganization and emptiness.

The analysis of the networks' regional distribution showed that, in participants with high scores in the disorganization dimension, a network characterized by a lower number of frontal brain regions and a higher number of temporal brain regions could be observed. This disorganization network can therefore be considered to be predominantly composed of temporo-temporal white matter fiber tract connections, while the emptiness network was characterized by a mainly proportional involvement of frontal, temporal, parietal, and occipital brain.

No interactions were found, however, when studying the relationship between subnetwork-specific white matter connectivity strength in the previously identified subnetworks and the patients' diagnosis. These findings further highlight the need to shift the focus from diagnosis to specific

psychopathological syndromes.

### Overlap of newly identified FTD-relevant networks with already known FTD-related brain regions in schizophrenia

In schizophrenia patients, several brain regions have already been characterized as associated with FTD in MRI studies conducted by various research groups. Consequently, in a next step, the researchers compared twenty-four of these brain regions to those regions found to be part of the identified FTD-relevant networks. This analysis confirmed that 38% and 28% of brain regions involved in the disorganization and emptiness subnetwork, respectively, spatially coincided with previously identified FTD-relevant brain regions and thus significantly more regions than would be expected for a randomly selected set. The brain regions identified included ones that had previously been associated with FTD symptoms in schizophrenia patients, but also regions known to be relevant for speech production and processing in the healthy population. All results remained significant after correcting for medication use and disease severity.

Still, the results must be interpreted with some caution. Nerve fiber tracking based on diffusion MRI imaging allows for noninvasive in vivo studies but entails the risk of significant modeling errors. However, this limitation is common among studies that rely on the same methodological approach. Other limitations of the present study include the fact that the researchers could not account for lifetime cumulative, but only for current intake of psychotropic medications.

### Conclusion

The researchers thus provide the first evidence for the long-debated hypothesis that FTD dimensions, such as disorganization, have a common structural connectome correlate across disorders, and not only related to schizophrenia as previously believed. Furthermore, their results indicate that the presence of FTD is correlated with dysconnectivity in specific subnetworks across all diagnoses, as connectome alterations spatially overlap in the brains of major depressive disorder, bipolar disorder, and schizophrenia patients. ●

#### The researchers

Tilo Kircher is a Professor of Psychiatry, Chair of the Department of Psychiatry and Psychotherapy, University of Marburg, Germany, and a Principal Investigator at the Center for Mind, Brain and Behavior at said university. Frederike Stein is a postdoctoral researcher at both institutions.

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