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# Is formal thought disorder in schizophrenia related to structural and functional aberrations in the language network? A systematic review of neuroimaging findings

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## ABSTRACT

Formal thought disorder (FTD) is a core feature of schizophrenia, a marker of illness severity and a predictor of outcome. The underlying neural mechanisms are still a matter of debate. This study aimed at 1) reviewing the literature on the neural correlates of FTD in schizophrenia, and 2) testing the hypothesis that FTD correlates with structural and functional aberrations in the language network.

Medline, PsychInfo, and Embase were searched for neuroimaging studies, which applied a clinical measure to assess FTD in adults with schizophrenia and were published in English or German in peer-reviewed journals until December 2016.

Of 412 articles identified, 61 studies were included in the review. Volumetric studies reported bilateral grey matter deficits ( $L > R$ ) to be associated with FTD in the inferior frontal gyrus, the superior temporal gyrus and the inferior parietal lobe. The same regions showed hyperactivity in resting state functional magnetic resonance imaging (fMRI) studies and both hyper- and hypoactivity in fMRI studies that employed semantic processing or free speech production tasks. Diffusion tensor imaging studies demonstrated white matter aberrations in fibre tracts that connect the frontal and temporo-parietal regions.

FTD in schizophrenia was found to be associated with structural and functional aberrations in the language network. However, there are studies that did not find an association between FTD and neural aberrations of the language network and regions not included in the language network have been associated with FTD. Thus, future research is needed to clarify the specificity of the language network for FTD in schizophrenia.

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## 1. Introduction

Formal thought disorder (FTD) is a core symptom of schizophrenia. 'Formal' refers to aberrations in the thought process in contrast to aberrations in the thought content (i.e., delusions). As FTD affects the thought process as well as thought expression, it is defined as a severe language and speech disturbance (Hart and Lewine, 2017). It occurs in the general population (Rossler et al., 2013), in relatives of patients with schizophrenia (Morgan et al., 2017), in people at high risk of developing psychosis (Demjaha et al., 2012; Katsura et al., 2014), as well as in patients with non-affective psychoses, affective psychoses, and nonpsychotic disorders (Nagels et al., 2016). Prevalence rates, which are dependent on the assessment method used, are highest in schizophrenia (50–80%), followed by schizoaffective disorders (60%), depression (53%), and healthy controls (6%). The results regarding the prevalence in mania are mixed, with some studies reporting higher rates and

**Abbreviations:** AF, Arcuate Fascicle; AG, Angular Gyrus; ASL, Arterial Spin Labeling; BA, Brodmann Area; BOLD, Blood-Oxygen-Level Dependent; BPS, Bern Psychopathology Scale; CBF, Cerebral Blood Flow; CT, Computer Tomography; DTI, Diffusion Tensor Imaging; FA, Fractional Anisotropy; fMRI, functional Magnetic Resonance Imaging; FOp, Frontal Operculum; FTD, Formal Thought Disorder; GM, Grey Matter; HC, Healthy Controls; HG, Heschl's Gyrus; IFG, Inferior Frontal Gyrus; ILF, Inferior Longitudinal Fascicle; IFOF, Inferior Fronto-Occipital Fascicle; IPL, Inferior Parietal Lobe; MdLF, Middle Longitudinal Fascicle; MRI, Magnetic Resonance Imaging; MTG, Middle Temporal Gyrus; PET, Positron Emission Tomography; RDoC, Research Domain Criteria; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; ROI, Region Of Interest; SLF, Superior Longitudinal Fascicle; SMG, Supramarginal Gyrus; sMRI, structural Magnetic Resonance Imaging; SPECT, Single Photon Emission Computer Tomography; STG, Superior Temporal Gyrus; STS, Superior Temporal Sulcus; SZ, Schizophrenia; TALD, Thought and Language Disorder Scale; UF, Uncinate Fascicle; WM, White Matter.

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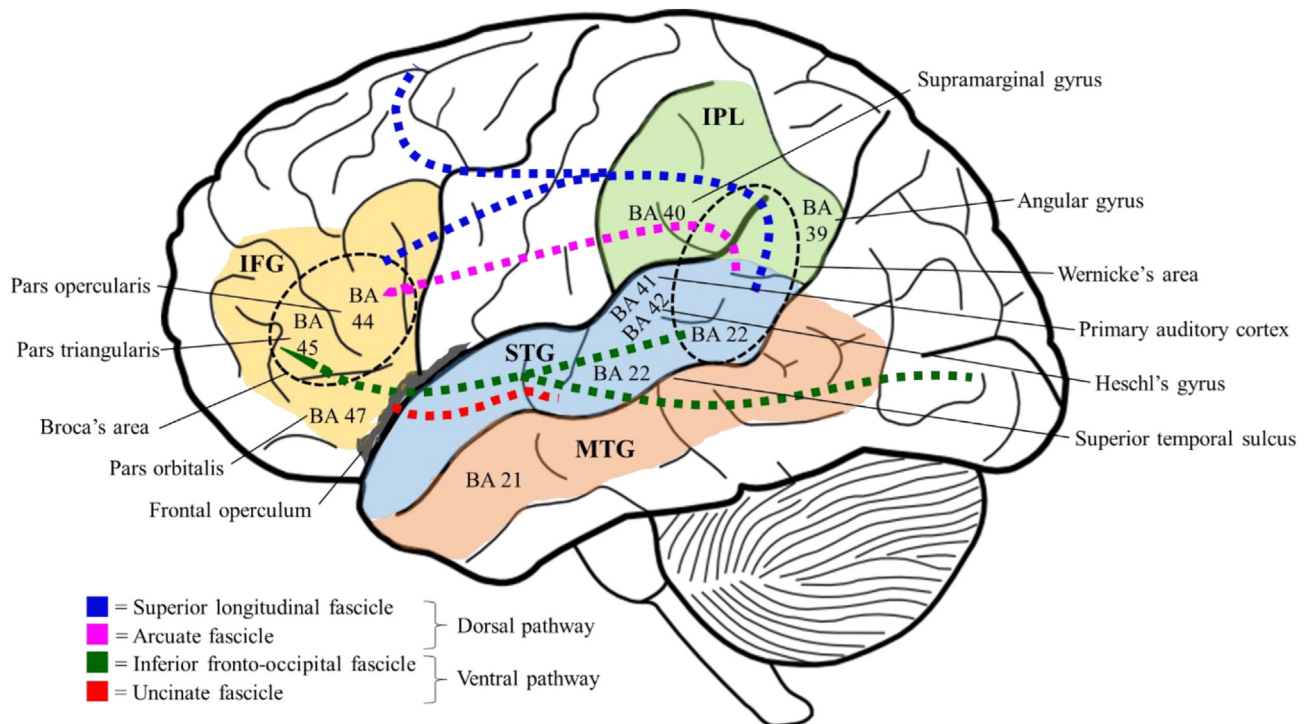
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other studies reporting lower or similar rates than in schizophrenia (Roche et al., 2015). Therefore, FTD should be considered as both a dimensional entity of language pathology and a categorical entity in terms of a trait marker for psychosis (Roche et al., 2015). Further, FTD is multidimensional and has been distinguished into quantitative (e.g., speed of speech, poverty of content of speech) and qualitative (e.g., neologisms, semantic and phonemic paraphasia), objective (e.g., observer-rated circumstantiality, cross-talk) and subjective (e.g., self-reported inhibited thinking, pressure/rush of thought), and positive (e.g., derailment, tangentiality) and negative (e.g., poverty of thought, thought blocking) forms (Kircher et al., 2014; Strik et al., 2010). For illustrative speech examples of patients with FTD, see Andreasen (1979). Usually, FTD is assessed by clinician-based rating scales, which demonstrated adequate psychometric properties and clinical utility (for an overview about common ratings scales, see Hart and Lewine, 2017). Recently, the usage of alternative approaches such as behavioural coding of communication failures, computational linguistic methods or ambulatory recording technologies have been proposed in order to overcome the limitations of the traditional clinical scales (e.g., questionable inter-rater reliability, low ecological validity; Cohen et al., 2017; Elvevag et al., 2017). Positive and negative FTD have distinct neuropsychological (Nagels et al., 2016; Tan and Rossell, 2017) and neurobiological correlates (Palaniyappan et al., 2015; Sans-Sansa et al., 2013), and negative FTD proved to be a better predictor of clinical and functional outcome than positive FTD (Roche et al., 2015). Overall, FTD is disabling, limiting symptomatic remission (Yalincetin et al., 2016b), social and occupational functioning (Tirupati et al., 2004; Yalincetin et al., 2016b), wellbeing and life satisfaction (Sigaudo et al., 2014; Tan et al., 2014), and therapeutic relationship and psychological recovery (Cavelti et al., 2016).

Language processing is served by cortical and subcortical cerebral networks. Disturbed communication within and between brain regions of the language network may constitute the neurobiological underpinnings of FTD (Kircher, 2008; Strik et al., 2008). Being aware that the neural network underlying human language comprises multiple and widespread regions throughout the brain, the “language network”

traditionally refers to the inferior frontal gyrus (IFG; approx. Brodmann Area (BA) 44, 45, 47), the frontal operculum (FOP), the superior temporal gyrus (STG; approx. BA 22, 38, 41, 42), the middle temporal gyrus (MTG; approx. BA 21, 37), the superior temporal sulcus (STS) and the inferior parietal lobe (IPL; approx. BA 39, 40) of both hemispheres (L > R; see Fig. 1). Additional cortical regions across the brain are recruited for language perception (i.e., sensory input systems such as the auditory system (Heschl's gyrus (HG) in the superior temporal lobe for hearing and the visual system (visual word form area) in the temporo-occipital region for reading) and speech production (i.e., premotor cortex and supplementary motor area in the frontal lobe for articulation), respectively (Price, 2010). The communication between the grey matter (GM) regions of the language network is accomplished by white matter (WM) fibre bundles. The frontal and temporo-parietal language regions are connected by a dorsal and ventral pathway, respectively (Friederici, 2011; Hickok and Poeppel, 2007). The dorsal pathway includes the arcuate fascicle (AF) and the superior longitudinal fascicle (SLF), while the inferior fronto-occipital fascicle (IFOF) and the uncinate fascicle (UF) are major fibre tracts of the ventral pathway (Chang et al., 2015; Friederici, 2011). Additional WM tracts involved in language processing are the middle longitudinal fascicle (MdLF), which connects anterior and posterior temporal regions, and the inferior longitudinal fascicle (ILF), which connects the temporal pole to the occipital lobe (Chang et al., 2015) (for a more detailed description of the anatomy of the language network we refer to excellent reviews by Price (2010) and Friederici (Friederici, 2011, 2012; Friederici and Gierhan, 2013)).

Strik et al. (2008) proposed that in periods of increased demands for communication performance (e.g., during critical life events or transitions into the next stage of life), GM deficits in temporo-parietal regions of the left hemisphere (Horn et al., 2010) may trigger a dysfunction in the bilateral language network, including the IFG, STG and IPL (Horn et al., 2009; Horn et al., 2012; Stegmayer et al., 2017). This dysfunction of the language network may be mediated by aberrations in WM tracts of the language network (UF, SLF, ILF, IFOF) and the corpus callosum, which is the major connection between the two hemispheres of the brain (Viher et al., 2016b). As a result of these structural and functional



**Fig. 1.** Schematic illustration of the major cortical regions and white matter tracts of the language network in the left hemisphere ((adapted from Friederici, 2011, 2012; Friederici and Gierhan, 2013; Price, 2010)). Notes. BA = Brodmann Area, IFG = inferior frontal gyrus, IPL = inferior parietal lobe, MTG = middle temporal gyrus, STG = superior temporal gyrus.

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