Language Network Dysfunction and Formal Thought Disorder in schizophrenia

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Abstract

Background

Pathophysiological inquiries into schizophrenia require a consideration of one of its most defining features: disorganisation and impoverishment in verbal behaviour. This feature, often captured using the term Formal Thought Disorder (FTD), still remains to be one of the most poorly understood and often understudied dimensions of schizophrenia. The large-scale network level dysfunction that contributes to FTD remains unclear to date.

Design

In this narrative review, we consider the various challenges that need to be addressed for us to move towards mapping FTD (construct) to a brain network level account (circuit).

Results

The construct-to-circuit mapping goal is now becoming more plausible than it ever was, given the parallel advent of brain stimulation and the tools providing objective readouts of human speech. Notwithstanding this, several challenges remain to be overcome before we can decisively map the neural basis of FTD. We highlight the need for phenotype refinement, robust experimental designs, informed analytical choices, and present plausible targets in and beyond the Language Network for brain stimulation studies in FTD.

Conclusions

Developing a therapeutically beneficial pathophysiological model of FTD is a challenging endeavour, but holds the promise of improving interpersonal communication and reducing social disability in schizophrenia. Addressing the issues raised in this review will be a decisive step in this direction.

Keywords: speech disorder, syntax, computational linguistics, semantics, connectome, brain stimulation, TMS

Introduction

Nearly six decades ago, Meehl argued that psychotic speech is the 'diagnostic bell ringer' for schizophrenia [1]. On the other side of the Atlantic, when trying to decipher psychotic speech, Critchley noted with some frustration that the "neurology of psychotic speech forms a veritable *terra incognita*, a lush and unplotted jungle terrain" [2]. To navigate this terrain successfully, we need to delineate the functional architecture of psychotic speech (or formal thought disorder (FTD)). As a research endeavor, pursuing this aspect of schizophrenia holds the promise of uncovering the pathophysiology of adverse long-term prognosis that typifies this illness. In the last 30 years, modern imaging techniques have afforded the means to navigate into this 'lush jungle', but most parts of the terrain of FTD still remain incognito. This review attempts to chart the obstacles we face and the ways we have to circumvent them.

When mapping the neuroanatomy of FTD, two arguments have been put forward, extending the neuropsychological dyssemantic vs. dysexecutive hypothesis of FTD to the neuroanatomical domain [3,4]. The first argument is that FTD, being a symptom expressed predominantly in the speech domain, essentially arises from a language network [LN] dysfunction [5,6]. The language network forms the neural substrate for human speech comprehension and production, both of which are disturbed in schizophrenia. The second argument is that FTD is essentially a cognitive disorder resulting from an executive dysfunction [7,8]. While the initial focus was predominantly on the prefrontal cortex [7,9,10], several anatomically distinct but distributed executive, attentional and social cognition networks are now recognised as contributors, placing constraints on how speech is contextually employed. To date it is unclear which of these large-scale network level (or macro-circuit) dysfunction is primary and thus essential and therapeutically relevant to reduce the burden of FTD. This paucity is somewhat surprising, given that the earliest theory-driven neuroanatomical studies in schizophrenia began with language dysfunction as the motivating framework [11,12][1].

In this work, we consider the challenges and opportunities in the pursuit of 'construct to circuit' mapping, i.e., relating FTD[2] to the language system. We consider precise network-level mapping as critical to develop empirical treatments (e.g., targeted neuromodulation, specific cognitive or linguistic remediation approaches) to alleviate persistent FTD, for which no therapeutic solutions exist to date. To this end, we present a narrative review, based on the primary studies included in four recent systematic reviews of imaging studies in FTD [15–18], and pursue the reports that cite these reviews (citations indexed in Google Scholar as of 31 July 2022).

Prior work on neuroanatomy of FTD

In pursuit of the neural correlates of FTD, several neuroimaging studies have related a rating scale measure of FTD to structural or functional neuroanatomical measures. Using a quantitative synthesis (Activation Likelihood Estimation) of the functional MRI studies addressing this question, Wensing and colleagues concluded that two left-sided language network clusters (superior and ventral posterior Middle

[1] Wernicke circa 1894: "any mental illness, insofar as it comes to light through a patient's incorrect spoken words, is, … an example of transcortical aphasia" [Wernicke: as translated in 13]

[2] Throughout this review, we use the term Thought Disorder, as it is the common parlance in imaging studies that investigate the construct of disorganised and impoverished speech in schizophrenia. Nevertheless, we acknowledge a number of outstanding issues in equating human language and thought [see Hinzen and Rossello [14] for one consideration of this issue in the context of schizophrenia].

Temporal Gyrus) are the most likely sites of aberrant activation in those with schizophrenia and more severe FTD [15]. Chen and colleagues later demonstrated that in those with more severe positive FTD, the resting-state connectivity between these language regions and the regions implicated in working memory (Middle Frontal Gyrus), social cognition (Inferior Parietal Lobule) is reduced [19]. Sumner separated structural studies (n=96; [17]) and the task-based fMRI studies that specifically focussed on executive, language, or semantic functions (n=35; [18]) for qualitative synthesis, reporting the involvement of orbitofrontal, cingulate, caudate and cerebellar regions (corticostriatal network) in addition to the core language network regions in FTD. In an extensive qualitative review of 61 studies of different modalities, Cavelti and colleagues found "moderate support for the structural and functional involvement of the language network in FTD in schizophrenia" [16].

These reviews highlight several shortcomings in the field. Sumner [18] in particular highlighted the lack of replicability and paucity of theoretically motivated studies in the symptom-circuit mapping exercise pertaining to FTD. Further, most studies have focussed on language regions/tasks, motivated by the semantic dysfunction hypothesis and thus biased to detect deficits in the LN, with very few studies directly studying the executive and other 'non-language' networks or examining the likely different substrates of positive and negative FTD. Furthermore, there are no studies that directly test competing neuroanatomical hypotheses to gather evidence to refute (*the refutation inertia*).

Thus, while the extant literature to date supports a role for the core LN in FTD, it does not conclusively rule out the role of other large-scale networks supporting attention, motor execution and social cognition. While it is tempting to accept a non-competing reconciliation that accommodates both arguments (i.e, both LN and non-language networks are equally affected in FTD), such nonexclusivity is likely to hinder progress in developing an explanatory account of FTD (see [20] on the problem of 'abductive logic' in schizophrenia). To move beyond this impasse, we first scrutinize the challenges in studying the construct (FTD: issues 1-3), the challenges in mapping the circuit (specifically the LN, given the prior focus to date: issues 4-6), and conclude with summarising the opportunities ahead of us.

Issue 1: The measured construct of FTD

FTD, as a psychopathological construct, is an observer's inference of a disordered thought process based on the speech of a subject. In this sense, it is not a symptom that is reported verbatim by the patient, as in the case of hallucinations or depression, but a clinical sign. But unlike other clinical signs e.g. responding to unseen stimuli, tremors, mannerisms, many of the features of FTD are extremes of normally encountered variations in language behaviours, with no defining cutoff for qualitative categorisation. For example, the degree of coherence, latency, verbosity etc., vary considerably among seemingly healthy individuals. Reliable inference of these signs as pathological *(judging the bizarreness issue)* is a considerable challenge, not fully solved by providing descriptors for rating scales or anecdotes, but can be improved with rules-based discourse analysis[21]. In addition to the noise inherent to clinical judgements ("wherever there is judgement, there is noise" [22]), an additional threat to reliable determination of FTD comes from bias arising from sociolinguistic and cultural differences [23] affecting how we define peculiarities in speech to rate FTD. Poor reliability reduces the likelihood of large effect size observations for validity measures (i.e. any FTD - brain metric correlations cannot be higher than the magnitude of correlation between two FTD raters [24]). See [25] where this issue is reported in detail.

Another challenge is that many studies seeking neural correlates of FTD have relied on either single item measurement of conceptual disorganisation or a composite score of FTD based on multiple items [18]. Following on the initial dichotomization of FTD by Fish (see [26] for an overview), factor analytic studies indicate that at least two (positive/disorganisation and negative/impoverishment), if not more[27], separable latent factors may account for these items [28]. Importantly, these factors appear to have distinct trajectories and treatment responsiveness [29,30], making it critical to parse these multiple factors and examine their neural correlates separately *(the collapsed dimensions issue)*.

Studies that purport to delineate the neural basis of FTD often relate the variance in the severity of FTD to the variance in the brain measure of interest. But, what does it mean to say that someone has a severe FTD? For most of the scales, the eventual severity score depends on the number of items observed or endorsed, and there is no consensus on the minimum number of mutually exclusive items required to capture the construct of severe FTD (e.g. 23 in Thought Disorder Index [TDI] [31] vs. 7 in Thought and Language Index [TLI] [32]). While some scales describe different types of FTD as items with differing weights based on their pathological nature (e.g. TDI), others provide grades for each descriptive item (e.g. Thought and Language Dysfunction Scale [TALD] [33]). Consequently, while some of the items (especially in the positive FTD domain) are highly correlated across the scales, several other critical items show modest or no overlap [33,34]. Further, when ordinally grading each item, rating scales may rely on the ease with which a phenomenon can be observed (e.g., poverty of speech item in TLI, most of the items in TALD), or the total portion of an interview for which it was observed (e.g. Clinical Language Disorder Rating Scale [35]), or the number of times that a phenomenon occurred (e.g. distractibility in TLI, Thought Language and Communication Scale [36]), or on the degree of functional consequences (Communication Disturbances Index [37]) that are thought to result from FTD. The neural correlates of each of these aspects may be distinct, reducing comparability for many, if not all FTD domains, among neuroimaging studies using different rating scales *(the severity grading issue)*. Recording and transcribing FTD interviews will improve comparability and enable the use of multiple rating scales.

Finally, clinicians and trained raters can only observe speech but not thoughts; but we have to assume an identity between the two (*the inferential gap issue*). Chaika called for the term ‘Thought Disorder’ to be abandoned in favor of speech disorder [38], while others provide evidence countering this argument [39]. This consideration is important as certain items in FTD scales may tap on language domain more directly, and thus have a higher likelihood of mapping on to the LN dysfunction (e.g., phonemic paraphasia) than the others (e.g., distractibility, thought interference or repetitive behaviour [40]). Psychopathological factors representing the latent processes contributing to FTD can be recovered from computational models based on certain theoretical frameworks (e.g., active inference[41]).

Issue 2: The varying course of FTD

A major challenge in construct-to-circuit mapping is the ability to separate state from trait variations. This is an important issue for FTD, as certain aspects of FTD are state-like (e.g. verbosity and disorganization dimensions that vary with affect [42,43]) while others such as poverty and idiosyncrasies of speech are more trait-like and stable throughout the illness trajectory [44]. Before overt psychotic features arise, both subthreshold positive and negative FTD features can be seen in prodromal or at-risk subjects [45–48]. In acute stages of illness, positive FTD is more prominent, and appears to be a transdiagnostic feature [40,43], though the later persistence of positive [28] as well as negative FTD [49] is more likely to occur

in schizophrenia. Furthermore, pharmacological manipulations with dopaminergic agents recover the state-like features more reliably than trait-like features (see [50] for a review). Taken together, the neural correlates of persistent trait-like features may map on to the vulnerability (or diathesis) for FTD and the construct of schizophrenia more broadly, unlike the correlates of acute FTD (*time-varying symptoms issue*).

Longitudinal studies could not only address this issue, but also uncover the neural correlates of resolution of severe FTD, of which we have scarcely any knowledge at present. In cross-sectional investigations, the state and trait-related variations in FTD severity is confounded and the nature of FTD's relationship to LN dysfunction may be obscured. One approach to address this, suggested by Mathalon and Ford [51] on the basis of psychometric literature, is to average symptom scores over time to determine trait-like severity around which an individual's scores may fluctuate. Another approach is to estimate persistence of FTD features in a retrospective manner in cross-sectional studies; most FTD rating scales do not consider persistence over time whilst rating FTD features. Finally, studying florid thought disorder in acute psychosis using imaging paradigms is a major challenge. For this reason, most studies have sought clinically stable samples. Technical advances that enable mobile recording and approaches that reduce acquisition time [52,53] may offer a better window into acute FTD.

Issue 3: Controlled experimental generation of FTD

One of the limitations in studying FTD as a construct is the lack of reliable means to evoke FTD in a controlled and periodic manner, unlike obsessions that can be provoked, and depressive mood that can be induced reliably [54,55]. Estimating the timing of the occurrence of aberrations that characterize FTD is not feasible as subjective perception of discrete instances of disorganized thinking is elusive to most subjects (unlike hallucinations where button press approach to symptom capture is realistic [56]). Pharmacological provocation with ketamine and stimulants is one option, but concerns about the safety of this approach in patients with schizophrenia continues to restrict its utility [57,58] (*the symptom capture challenge*). One naturalistic alternative to drug-challenge studies is dose reduction or treatment discontinuation studies; especially in first-episode samples, clinician-guided trials of antipsychotic discontinuation are becoming increasingly common [59,60]. This may offer a window to study within-subject changes in the severity of FTD. Further, careful experimental manipulation of context can influence FTD, especially when quantified on the basis of discourse level linguistics [61].

Time locking in-scanner recording of idiosyncratic utterances during descriptive speech production is one option, if the challenges related to motion artifacts during speech can be satisfactorily addressed. Computational linguistic approaches (see below) can provide parameters that can be studied in an event-related manner with fMRI/MEG, providing a promising way forward [62]. Hyperscanning experiments may allow the assessment of interbrain synchrony in LN activation during conversational paradigms [63]. Several experimental challenges need to be overcome to realize these goals.

Issue 4: Specificity of LN dysfunction to FTD

Prior studies have placed a strong emphasis on the LN when studying FTD. Presence of FTD is an indicator of overall illness severity and persistence [64]. As a result, the neural correlates of FTD may indeed be non-specific indicators of overall illness severity, other covarying symptoms (such as hallucinations), and the treatments instituted to alleviate the overall severity [65]. Structural and

functional studies of AVH also map on the LN regions, indicating potential non-specificity when attributing LN dysfunction to FTD [66–68]. This confound is difficult to tease apart in studies seeking symptom-brain association studies. Seeking unmedicated or untreated early stage patients may provide a sample with sufficiently high illness severity while varying FTD burden. In one such early stage sample, Dey and colleagues reported reduced global connectivity of a right STG/insula cluster (with a strong connectivity to the LN); this was a feature of schizophrenia, rather than the severity of FTD [69]. Aberrant connectivity of the LN nodes appears to be a notable feature in drug-naive samples with both short and long duration of illness, irrespective of their symptom burden [70]. DeLisi and colleagues have demonstrated in multiple studies that LN aberrations are a feature of the genetic risk of schizophrenia [71–73]. Thus, we cannot dismiss the probability of LN dysfunction being a general feature of schizophrenia, not restricted to those with severe FTD alone (*confounded diagnostic effect*).

A counterfactual to the above conclusion can come from observing FTD-LN relationship in the absence of schizophrenia. Two large transdiagnostic symptom mapping studies of FTD have been reported in recent times, drawing on the same FOR2107 cohort of n=1071 patients [74]. In whole-brain exploratory analyses relating gray matter volume and white matter integrity to positive FTD (derived from a multi-scale factor analysis) and FTD-scale specific positive (disorganisation, incoherence) and negative FTD factors (emptiness), Stein and colleagues report associations outside of the core LN (right middle frontal gyrus, left middle occipital gyrus, anterior thalamic radiation and right posterior cingulum) [75,76]. Conventional language regions do not appear prominent in these transdiagnostic analyses even when a spatially-focussed analysis is attempted [76].

Taken together, these studies indicate the lack of one-to-one correspondence between FTD and LN structure/function. In fact, the relationship between LN dysfunction and FTD may be restricted to schizophrenia, where it may be confounded by other symptom domains (e.g. AVH) (*symptom overlap issue*). Reporting symptom level covariance within clinical samples, and studying both shared and distinct construct-to-circuit associations, examining transdiagnostic and non-clinical samples with FTD, and using rating approaches that reduce the effect of global impression on symptom scores will be critical to establish claims of specificity.

Issue 5: The challenges of delineating the LN

Construct to circuit mapping efforts relating to LN are particularly challenging due to the spatial nature of LN and the debate surrounding its constituent parts. While there is a broad agreement that a left lateralized peri-Sylvian system is critical for language, the delineation of a distinct neuroanatomical entity subserving all of the component parts of language as its specific function has been a considerable challenge [77–79].

Historically, specialized lateralized peri-Sylvian ‘epicenters’ and tracts connecting them were described as defining the LN [80]. Nevertheless, the core nodes of these epicenters were variously defined and are not seen as natural anatomical kinds [78,81]. Later extensions of the margins of the LN based on burgeoning interest in neurolinguistics have reduced its spatial precision, resulting in a LN concept that is too broad to test specific hypotheses about symptom construct relationships [79]. While the existence of a dual - ventral and dorsal stream - connectional architecture constituting the core LN is well described [82], their function and connectivity remain controversial [83–85]. It is now recognised that the LN spatially overlaps with several other association networks [86], despite maintaining considerable functional

selectivity for processing essential aspects of human language [87,88]. Thus, concurrent with the realization that multiple brain networks are crucial for our language behaviour [89], more anatomical precision has been emerging in defining the core LN and constituent parts [90]. For our purposes of mapping FTD to LN, it is essential to leverage this emerging anatomical precision.

Using a predefined anatomical atlas to identify a common LN is fraught with the issue of notable between-subjects variability. The anatomy-function correspondence is poor for many association networks [91], and this problem appears to be particularly pronounced for language tasks (*spatial variability issue*) [92]. For psycholinguistic studies of language employing fMRI, one successful approach to overcome this issue has been the use of localiser scans to delineate a subject-specific LN before undertaking group-level analyses [93,94]. Localiser approaches for the LN have predominantly relied on reading sentence vs. sequence of non-words contrast, though articulation-sensitive [95] and naturalistic tasks can also be used [96]. Localiser approaches have been used in studies on hallucinations (see for example [97]); employing this approach in studies of FTD will improve the precision of mapping LN to FTD.

Issue 6: Compensatory neural changes

LN shows a particular capacity for plastic adaptation to damage, in part due to a high degree of degeneracy in representation that confers robustness to damage [98]. The adaptive changes in LN are apparent during the normal ageing process where despite sensorimotor decline, language processing remains stable with novel brain regions recruited in its service [99], and after vascular damage, where non-dominant homologues come into play [100].

If we assume schizophrenia as a disorder that involves some degree of illness-related brain changes, then concomitant adaptive changes in response to this deficit should be expected, at least in a subset of patients [101,102]. Some of these adaptive changes, in effect, may obscure the construct-to-circuit relationship between the LN and FTD. In part, this is due to the increase in inter-individual variability of brain changes introduced by the putative compensatory process [103], affecting our ability to successfully relate FTD to LN dysfunction. In a recent work examining quantitative MR signals, Wei and colleagues observed an overall increase in periSylvian intracortical myelin signal among drug-naive patients with first episode schizophrenia compared to healthy subjects [104], but this increase was pronounced in patients with lower levels of disorganization. Thus, patients with lower FTD burden may have a marked (putative) compensatory increase in myelin in the LN which fails to occur in those with higher FTD. Similarly in a 7T multivariate study, Palaniyappan and colleagues reported increased frontocingular grey matter volume (GMV) in relation to higher negative FTD burden, alongside reduced GMV in striatum, insula and precuneus [105]. While the neurobiological interpretation of increases and decreases of GMV in MRI is still elusive, the concurrent presence of both in a structurally covarying set of brain regions indicate the possibility of an adaptive process or reorganization. Also see [69] and [106] for further support for compensatory brain changes in relation to FTD (*the adaptive changes issue*).

We cannot determine if a brain change is truly compensatory (and thus secondary and adaptive) without having a longitudinal assessment of both symptoms and the suspected neural substrate. From cross-sectional studies, only putative inferences can be drawn by using multivariate or connectomic approaches such as structural covariance analyses. Unfortunately, no study to date has reported on

longitudinally tracked FTD in conjunction with multiple time points of brain imaging data. Such longitudinal studies are critical to establish whether LN dysfunction continues to relate to FTD over time (within subject variations), tracking the changing burden of positive and negative FTD.

Future directions

Moving beyond rating scales for FTD

How do we move towards more sensitive detection and reliable rating of the FTD construct? Increasingly, computational linguistic approaches are being used for NLP, providing an objective means to quantify subtle deviations and idiosyncrasies in speech using recorded readouts [107–111]. These measures can be derived from speech samples across various contexts - social, written texts, media posts, video interviews, and descriptive speech inside a scanner thus obviating the need for a one-to-one clinical interviewing for rating [112,113]. Hypothesis driven studies utilizing such automated measures in conjunction with brain imaging have already shown promising results, providing leads for readouts that can be employed in focal perturbation studies [114–117]. As these syntactic (e.g. mean length of a sentence, number of connectives) and semantic (e.g. similarity between words) measurements are more intuitively aligned to cognitive linguistics than rating scale items (e.g. concretism, logorrhea etc.), adapting this approach may uncover the hitherto elusive link between FTD and LN.

Despite this success, it is important to note that the number of automated linguistic features that can be extracted is very large, introducing high researcher degree of freedom [118], and a large feature space that may inadvertently enable multiple-testing and p-hacking issues in association studies if a priori choices are not made (*appropriate predictor issue*). While these issues can be addressed to some extent via planned dimension reductions and pre-registration of the model space, such efforts need a priori principles for the proposed choices. Extensive clinical calibrations with qualitative measures of FTD (i.e., establishing the NLP feature(s) that consistently relate to known constructs of FTD, measured using state-of-art clinical instruments at an aggregate and individual level) are required to guide feature selection for mechanistic studies [119]. Without such calibrations, many successful multivariate NLP models may appear, but without sufficient ability to justify how they classify an individual to have FTD. As Andreasen elegantly put, “technology without the companionship of wise clinicians with specific expertise in psychopathology will be a lonely, sterile, and perhaps fruitless enterprise” [120]. Secondly, a computational linguistic readout may mathematically formalise the aberrant language behavior in FTD, but it does not in itself clarify the physiological steps needed to produce it, or the ways in which the LN realizes these steps. A generative model of how brain activity results in FTD is required to fill this gap (see [121,122]). Third, when using NLP approaches in psychosis, FTD is a latent (or hidden) psychopathological construct that we purport to measure using quantifiable linguistic readouts; the relationship between the parameters of the latent construct and the observational data needs rigorous model based testing, ideally in terms of comparing the evidence for competing models. This is a challenge that can be tackled within the emerging framework of computational psychiatry [41].

Moving beyond network mapping by association

Different human brain mapping approaches provide varying degrees of support for causal inferences for behavioral outcomes [123]. Most of our present knowledge linking LN to FTD comes from inferences based on incidental atrophy of gray matter or disruption of white matter, or from manipulating behavior (task performance) to observe brain changes (BOLD signal or ERP studies); both of these approaches do

not provide sufficient grounds for a causal association (*the weak causal mapping issue*) [123]. Manipulating brain activity and observing its effect on language behavior, will strengthen causal inferences. Many LN and non-language sites (the temporo-parietal junction, inferior parietal lobe (social cognition network), inferior frontal gyrus and superior or middle temporal gyrus (language), middle frontal gyrus (executive), anterior prefrontal cortex (salience) and the cerebellum [Figure 1]) are well established as safe targets for transcranial magnetic stimulation (TMS) for positive[124,125] and negative symptoms [126]; these offer feasible targets to study causal circuits of FTD (Figure 1).

We see two distinct translational benefits from overcoming the issues listed in Table 1 to achieve a rigorous and decisive causal circuit-to-construct mapping for FTD. First, prognostication in early psychosis (i.e. identifying those who will have persistent FTD) may be feasible by identifying specific macro-circuit deficits. Second, noninvasive brain stimulation, metacognitive approaches of cognitive remediation [127], training in communication pragmatics [128], speech-gesture training [129], expressive-discursive skills training [130] are various options that can be grouped together as approaches of Language Network Modulation - a novel therapeutic means to address a hitherto unmet burden of disorganization that typifies the progressive nature of schizophrenia (described as "a drift towards disorganisation" by [131]). Matching patients to these treatments, selecting appropriate stimulation targets and predicting treatment response[132] can be achieved with precise causal mapping of the FTD-related macro-circuit deficits.

FTD - an exemplar case for in vivo mechanistic pursuits in schizophrenia

The study of diagnosed cases vs. non-cases using neuroimaging has not provided actionable clinical solutions in the study of schizophrenia to date [133,134]. The presence of genetic heterogeneity[135,136] has prompted calls for a continuum approach to symptoms; nevertheless, symptom dimensions may be as complex as diagnostic constructs [137], and continuum models face the vexing curse of dimensionality [138]. Amassing large samples may not overcome this issue; motivated selection and refinement of high-yield phenotypes is urgently needed [139].

Focussing on FTD provides two approaches to address this conundrum in schizophrenia. FTD is a fairly circumscribed but richly characterised phenotype that may have a higher chance of mapping onto distinct biological substrates. As a symptom domain, it appears to have a stronger genetic basis than other domains[140,141], and is highly pathognomonic for psychosis. Secondly, disorganised speech can be assessed without the need for a self- or observed-based assessment of 'mental state'. In this context, it differs from delusions, hallucinations, anhedonia, apathy etc. that rely on self reports of mental state or an observer's empathetic ability to understand another person's mental phenomenon. Thus, FTD presents an exemplar domain for potentially precise 'mathematical psychopathology', opening an opportunity for rigorous phenotype refinement.

With a burgeoning interest in NLP, computational models and the availability of digitally acquired data, we are at the cusp of reinvigorating the study of language in schizophrenia [142]. In the near future, we can anticipate the field to move beyond cross-sectional, correlational and discovery-focussed studies to longitudinal studies with 'perturb-and-measure' approaches testing competing hypotheses in appropriate clinical samples, with theoretically-motivated choice of NLP approaches. Large scale data-sharing efforts and open databases of recorded speech and imaging data will greatly hasten this enterprise [143].

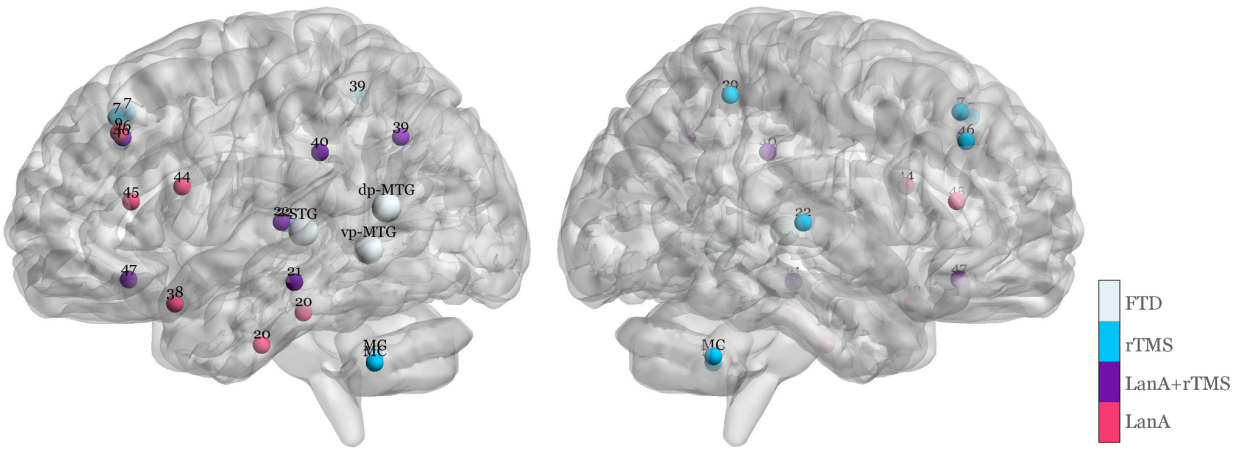

Figure 1: Most probable non-invasive brain stimulation targets for FTD. Pink nodes represent core language areas based on a probabilistic Language Atlas (LanA [144]). Blue nodes are rTMS stimulation sites used in prior clinical trials in schizophrenia, summarised from two recent meta-analytical syntheses [124,126]. The purple nodes represent an overlap between the blue and pink nodes (LanA+rTMS), thus providing possible sites for applying rTMS for perturb-and-measure causal mapping and clinical trials aimed at Language Network Modulation in schizophrenia. Three more regions (pale blue) represent the coordinates identified from the activation likelihood estimation analysis of studies investigating Formal Thought Disorder (FTD), as reported by Wensing and colleagues[15]. Of these 3 nodes, the Superior Temporal Gyrus (STG) node overlaps closely with site 22 of LanA+rTMS set. The numbers indicated as labels denote Brodmann's numbering conventions. MC: Medullary Cerebellum. dp-MTG: dorsal posterior Middle Temporal Gyrus, vp-MTG: ventral posterior Middle Temporal Gyrus.

Table 1: Challenges and probable solutions in circuit (LN) - to - construct (FTD) mapping

Issues/Challenges identified	Possible solutions to address the identified issues
The refutation inertia	● State and test competing network level hypotheses
The judgement of bizarreness issue	● Employ rules-based analysis of discourse ● Use objective readouts to quantify speech disruption
The collapsed dimensions issue	● Measure multiple component factors of FTD ● Seek factor-specific construct/circuit associations
The severity grading issue	● Use objective speech readouts ● Record and transcribe FTD interviews ● Relate frequency, intensity and impairment scores separately with imaging measures
The inferential gap issue	● Estimate parameters from computational models of disorganisation ● Report correlates of objective readouts (e.g. word counts) in addition to inferred ratings (e.g. reduced spontaneity)
The time-varying symptoms issue	● Longitudinal design ● Averaging symptom scores across time (for trait-like values) ● Separate acute and chronic phases of illness
The symptom capture challenge	● Using objective readouts with in-scanner speech recording ● Withdrawal challenge in patients ● 2-person studies (hyperscanning)
The confounded diagnostic effect	● Examine diagnostic effect independent of symptoms ● Seek transdiagnostic samples
The symptom overlap issue	● Examine & report covariance among symptom domains
The spatial variability issue	● Using subject-specific localiser approaches
The adaptive changes issue	● Longitudinal design with multiple time points of brain/behaviour data
The refutation inertia	● State and test competing network level hypotheses
The appropriate predictor issue	● Clinical calibration of NLP variables ● Test formal models linking NLP parameters with FTD ● Pre-register model space and dimensionality reduction
The weak causal mapping issue	● Perturb-and-measure studies

*NLP - Natural Language Processing FTD - Formal Thought Disorder

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