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Commentary on "Lower speech connectedness linked to incidence of psychosis in people at clinical high risk": The promise of graph theory and network neuroscience

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In this issue of Schizophrenia Research, Spencer and colleagues (Spencer et al., 2020) have published the first study that uses speech graph analysis to identify linguistic features that not only discriminate the language of individuals with psychotic disorder from the norm, but which also predict later psychosis onset in individuals identified as at clinical or ultra-high risk (CHR/UHR) for psychosis. This is the fourth study of its kind, that uses computational natural language processing (NLP) to identify language features that predict psychosis among CHR/UHR. The prior studies all relied on the semantic value of words, either to determine fluctuations in topic and meaning in spoken language (Bedi et al., 2015; Corcoran et al., 2018), or to evaluate both the specific semantic content (words related to "voices and sounds") and density of ideas within spoken sentences (Rezaii et al., 2019). For these prior approaches that involve semantics, a very large corpus of text must be available so that the algorithm can learn the meaning of words through their co-occurrence with other words.

Speech graph analysis is unique among computational NLP methods in that it is not corpus-based, such that patterns of "connectedness" can therefore be analyzed in any language, even those that do not yet have large corpuses established for analysis. Instead, it relies on the mathematical construct of graph theory, which informs the broader field of "network neuroscience" (Bassett and Sporns, 2017) now applied to the study of behavior at multiple levels of analysis, from molecules to communities.

A layman's understanding of graph theory might be best achieved through reviewing its curated Wikipedia page, which describes "graphs" as "the mathematical structures used to model pairwise relations between objects". The pairwise relations are between nodes (also called points or vertices); the connections between these nodes are called edges or links. Of note, in speech graph analyses, the nodes are words or lexemes, and the edges are the temporal links between words said in succession; speech graphs are "directed graphs" as there is a temporal flow of words. "Loops" are the series of edges that join a node back to itself; in speech, this would be the succession of words spoken before a specific word or lexeme is uttered again.

Graphs and networks have several properties that can be measured and described (reviewed in Mota et al. (2012)). The size of a graph is its total number of edges. Global attributes of graphs reflect the statistical properties of the network as a whole. These include the average "degree" of all nodes, where the degree of a node is the number of edges it has, and also includes density, which is the ratio of number of edges to the square of the number of nodes. In graphs and networks, average path lengths can be estimated as well as degrees of clustering among nodes.

Graphs can also be described in respect to "local" measures of "connectedness", which index the size of subgraphs or "connected components" (reviewed in Mota et al. (2012)). These have been operationalized as the "largest connected component" or LCC, which is the number of nodes in the largest "openly" connected subgraph, in which any pair of nodes can be linked by a path, and the "largest strongly connected component", or LSC, which is the number of nodes in the largest "closed" subgraph. In this issue's manuscript, these connectedness measures discriminated language in first episode psychosis and predicted later transition to psychosis among CHR/UHR individuals.

This manuscript is the latest in a body of work by Natália Mota that uses graph analytic software (Mota et al., 2014) to understand language, inspired by earlier work that showed that human language is a "small world network" with minimization of path distance (Cancho and Solé, 2001), and with hubs and clusters, enabled by the use of words that categorize (Sigman and Cecchi, 2002). In normal children, these measures of connectedness (e.g. LSC) in narrated stories about images recently seen were correlated with verbal short-term memory (Mota et al., 2020), IQ, and Theory of Mind, and predictive of later reading ability (Mota et al., 2016). Mota has shown that reduction in these measures of connectedness distinguish language in schizophrenia from that of mania (Mota et al., 2012), are highly correlated with negative symptoms and predict schizophrenia diagnosis among individuals with first episode psychosis (Mota et al., 2017), and represent a failure of maturation in schizophrenia (Mota et al., 2018). More recently, in collaboration with Lena Palaniyappan, Mota found these measures of connectedness were associated in psychosis with functional impairment, slowing of processing speed, and clinical ratings of thought disorder (Palaniyappan et al., 2019).

Strikingly, these speech connectedness features were also associated in psychosis with network properties of brain activity at rest, specifically variance in "degree centrality" of core hubs in the brain (Palaniyappan et al., 2019). As described above, a degree of a node is its number of edges; in the case of neuroimaging, the degree indexes the number of functional connections a voxel has to other voxels in the brain. Higher

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variance in degree centrality represents a weakening of core hubs in the brain with concomitant strengthening in peripheral hubs (Palaniyappan and Liddle, 2014). Remarkably, in earlier studies, Ralph Hoffman had shown in computer models that inducing a similar decentralization could lead to symptoms of schizophrenia, including disorder in language (Hoffman, 1997).

Graph theory has been used to assess circuit dynamics and to map connectivity and topology in brain networks (Power et al., 2011), including in schizophrenia, finding reductions in local network connectedness and modules (or subgraphs) (Fornito et al., 2012), analogous to what Mota has identified in her speech graph analysis of language in schizophrenia, specifically reduction in connectedness and subgraph size. Beyond speech and imaging, network analysis has also been applied to de novo mutations in schizophrenia in mapping these genes to known anatomy, developmental window of expression, and pathways (e.g. neuronal migration, synaptic transmission, signaling), suggesting disruption in fetal prefrontal cortical neurogenesis in schizophrenia.

The use of graph theory to describe attributes of networks in neuroscience has become a powerful tool across levels of analysis to understand behavior. In addition to speech/language, human brain activity and gene expression, network analysis can also be used to understand social interactions among individuals in a community or network (Bassett and Sporns, 2017). The real promise lies in using these powerful approaches together to study network dynamics and integration across levels of analysis so as to understand complex disorders such as schizophrenia. There is precedent for using network approaches to evaluate synchronization of brain activity across individuals during speaking and listening (Silbert et al., 2014), which may be informative for understanding the neural basis of the language impairments that characterize schizophrenia and predicts its onset among at-risk individuals.

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