# Introduction

Schizophrenia, or *split mind*, ranks among the most studied disorders in modern psychiatry and neuroscience. There are manifold reasons for this, but perhaps the two most prominent are the extent of its resultant social problems and the sheer variety of symptoms which it can produce. Symptoms of schizophrenia broadly fall into three categories, positive, negative, and cognitive, and can range from delusion, paranoia, and hallucination to apathy, anhedonia, and social withdrawal. This wide range of symptoms makes schizophrenia a difficult disorder to treat, as treatments for one group of symptoms may have limited or no effect on another. Indeed, it has been suggested that schizophrenia should not be considered a single disorder at all, but rather a family of disorders aggregated by historical precedent (Brodersen et al. 2014).

The dysconnectivity hypothesis has dominated schizophrenia research for the past quarter-century (Friston 1998). This hypothesis may be summarized as a proposition that aberrant connectivity is the primary cause of schizophrenia, not one or more focal abnormalities. In this sense, it may be considered a forerunner to the concept of distributed cognition—quite an early forerunner, as it was first proposed at the beginning of the 20th century (Wernicke 1906; Bleuler 1911; Moskowitz and Heim 2011). The past half-century of research into schizophrenia has amassed considerable evidence in its favor (Stephan, Baldeweg, and Friston 2006), with experimental results suggesting that schizophrenia affects connectivity and plasticity from the level of individual synapses (R. M. Allen and Young 1978; Javitt and Zukin 1991; Kapur 2003; Kreitschmann-Andermahr et al. 2001; Black et al. 2004) to interregional communication (Lawrie et al. 2002; Lee et al. 2003; Spencer et al. 2004) and white matter tracts. This preponderance of evidence has made it the dominant hypothesis in schizophrenia research today and has helped to solidify the broader theory of distributed cognition in the psychiatric and neuroscientific fields.

At the “global”, or whole-brain, scale, most studies have examined static functional connectivity (FC) or structural connectivity (SC). Such studies have reported reduced global connectivity in schizophrenia patients (Yu et al. 2012; 2015), particularly between auditory, sensorimotor, and visual networks (Damaraju et al. 2014). In addition, network-based analyses of schizophrenia functional connectivity indicate a general reduction in organization and efficiency in the structural and functional connectivity of schizophrenia patients (Kambeitz et al. 2016). Beyond this, however, findings have been inconsistent. Some reports suggest decreased communication between frontal and temporal areas of the brain (Lawrie et al. 2002); others have found increased connectivity within the default-mode network (Whitfield-Gabrieli et al. 2009); still others imply decreased connectivity within and between the default-mode network and cortical regions (Salvador et al. 2010). Attempts to model the static functional connectivity of schizophrenia patients have provided equally confused results, with both reduced effective connectivity and increased structural connectivity suggested (Cabral et al. 2012). Overall, then, analysis of structural and static functional connectivity has been unable to conclusively identify the large-scale changes which underly the symptoms of schizophrenia.

One potential reason for the inconclusiveness of static analyses is that they, by nature, neglect the dynamism of real brain activity. For decades, electroencephalography (EEG) has demonstrated that functional microstates constantly and fluidly change (Mutlu et al., 2012, Hennings et al., 2009; Koenig et al., 2002; Lehmann and Skrandies, 1984; Lehmann et al., 1998; Pascualmarqui et al., 1995), a fact which was captured in fMRI in 2010 (Sakoğlu et al. 2010; Chang and Glover 2010). Although fMRI captures microstate alterations at a timescale of seconds rather than the milliseconds of EEG, its superior spatial resolution compared to EEG allowed researchers to identify consistently recurring connectivity states (Hutchison et al. 2013; Preti, Bolton, and Van De Ville 2017; Calhoun et al. 2012; Yu et al. 2012; E. A. Allen et al. 2012) which may represent the building blocks of human information processing.

Schizophrenia patients have displayed altered dynamics of these states in previous studies. For instance, a 2014 study suggested that patients have a higher probability of entering states with attenuated cortical-subcortical connections and increased intra-sensory connectivity than controls, and that these same patients also display elevated low-frequency power in thalamo-sensory communication (Damaraju et al. 2014). This same study suggested that the thalamo-sensory hyperconnectivity reported in its static FC analysis may be an artifact of these alterations in state dynamics. However, aside from state transition probabilities and average dwell times, this study did not report any metrics designed to capture state dynamics. This lack of metrics designed to capture the dynamics of functional connectivity has proven a problem, not just for schizophrenia research, but for the broader field of functional neuroimaging.

This study begins to bridge that gap by applying a previously developed framework of measuring the entropy rate of individual fMRI scans (Blair et al. 2022) to the publicly available FBIRN dataset, which consists of medicated schizophrenia patients and demographically matched controls. This framework requires defining a basis for a state space within which to plot each subject’s time course. The decision to quantify state dynamics in a latent space is not entirely novel (Miller et al. 2016), but the present framework specifically seeks to define a basis, i.e. a minimal linearly independent spanning set, for this space to make most efficient use of the Shannon entropy. The results of this analysis suggest substantially disordered state dynamics in the patient population, with a specific tendency towards decreased predictability in three dimensions of the 171-dimensional state space. These three dimensions also correlate with certain clinical variables, which suggests that it may be possible to separate clinical subgroups within the basis space which this framework provides. Overall, this represents a positive step towards quantifying the dynamic connectivity alterations which underly psychiatric disease and towards the discovery of a clinically useful basis space in which to diagnose and predict patient treatment.