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Altered Brain Network Dynamics in Schizophrenia: A Cognitive Electroencephalography Study

Jodie Naim-Feil, Mica Rubinson, Dominik Freche, Alexander Grinshpoon, Abraham Peled, Elisha Moses, and Nava Levit-Binnun

ABSTRACT

BACKGROUND: Alterations in the dynamic coordination of widespread brain networks are proposed to underlie cognitive symptoms of schizophrenia. However, there is limited understanding of the temporal evolution of these networks and how they relate to cognitive impairment. The current study was designed to explore dynamic patterns of network connectivity underlying cognitive features of schizophrenia.

METHODS: In total, 21 inpatients with schizophrenia and 28 healthy control participants completed a cognitive task while electroencephalography data were simultaneously acquired. For each participant, Pearson cross-correlation was applied to electroencephalography data to construct correlation matrices that represent the static network (averaged over 1200 ms) and dynamic network (1200 ms divided into four windows of 300 ms) in response to cognitive stimuli. Global and regional network measures were extracted for comparison between groups.

RESULTS: Dynamic network analysis identified increased global efficiency; decreased clustering (globally and locally); reduced strength (weighted connectivity) around the frontal, parietal, and sensory-motor areas; and increased strength around the occipital lobes (a peripheral hub) in patients with schizophrenia. Regional network measures also correlated with clinical features of schizophrenia. Network differences were prominent 900 ms following the cognitive stimuli before returning to levels comparable to those of healthy control participants.

CONCLUSIONS: Patients with schizophrenia exhibited altered dynamic patterns of network connectivity across both global and regional measures. These network differences were time sensitive and may reflect abnormalities in the flexibility of the network that underlies aspects of cognitive function. Further research into network dynamics is critical to better understanding cognitive features of schizophrenia and identification of network biomarkers to improve diagnosis and treatment models.

Keywords: Cognition, Connectivity, Dynamics, Graph theory, Network, Schizophrenia

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Schizophrenia (SCH) is a complex and devastating psychiatric disorder whose underlying neurobiological mechanisms are still unknown. Cognitive dysfunction is a multifaceted and complex feature of SCH and is commonly associated with poor treatment outcomes (1). Many of these cognitive processes rely on brain circuitry such as the frontal and parietal regions (2), the same regions altered in SCH (3,4). Therefore, there appears to be an intricate relationship between cognitive impairment and the pathophysiology of SCH. The current study was designed to examine altered network connectivity patterns underlying various cognitive features of SCH and to explore the dynamic nature of these network anomalies.

Recently, topological measures that apply network analysis based on graph theory to neuroimaging data have been used to characterize global network properties of the brain (5–7). This approach is particularly pertinent to the study of SCH, which is described as the prototypical disease of brain dysconnectivity (8,9). Indeed, a growing number of studies have revealed network abnormalities in patients with SCH such as altered network measures of connectivity, efficiency, and integration (10). While these network findings are largely based on a static network representation of the SCH brain, there is a growing interest in the dynamic changes of network connectivity (11–13). Static network representations are derived from a network constructed by encapsulating neuroimaging data from an entire scan session (resting state or task activated). However, higher-order brain functions, such as executive function, require dynamic brain coordination that can occur on the order of milliseconds (14). To examine the dynamic connectivity changes that underlie specific features of cognition, recent studies in healthy control (HC) participants have applied network analysis to shorter time intervals and constructed functional networks for each of these time intervals to quantify how these networks change over time (15,16). Using this approach, recent functional magnetic resonance imaging studies have demonstrated dynamic reconfiguration of network connectivity patterns following administration of

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cognitive stimuli (13,17,18), while transient changes (on the order of seconds and milliseconds) in network states have been detected by magnetoencephalography (19) and electroencephalography (EEG) (14,20,21). Although network analysis traditionally has been performed on functional magnetic resonance imaging data, these EEG and magnetoencephalography studies highlight the temporal benefits of using physiological techniques to explore the rapid reconfiguration of functional brain networks underlying various aspects of cognition (20).

Given that impaired cognition is a key feature of SCH (1), the quantification of altered patterns of network connectivity underlying these deficits will help to identify aberrant global network properties of SCH (22–24). Preliminary EEG network (static) studies have demonstrated various network connectivity alterations across working memory (25–28) and auditory oddball (29) tasks in patients with SCH. The current study was designed to expand on these static network studies by applying dynamic network methodology and using the temporal advantages of EEG to explore the functional dynamic network organization underlying specific cognitive impairments associated with SCH.

To achieve this, we administered a robust and sensitive cognitive task called the Sustained Attention to Response Task (SART) (30). The SART provides a measure of response inhibition and sustained attention (31) and has been applied to identify clinically relevant cognitive impairments in patients with SCH (32–34). Successful performance on the SART requires activation of a number of widespread and spatially distributed brain regions in selecting and integrating those cognitive stimuli that are considered task relevant while suppressing irrelevant stimuli (35,36). In the current study, cognitive stimuli from the SART were used as a perturbation tool to elicit a transient change within the network organization while EEG measured the functional dynamics of the network response to the cognitive stimuli, thereby enabling us to quantify how these connectivity patterns differ in patients with SCH.

The current study had two major objectives: 1) characterize global properties of network connectivity (elicited by cognitive stimuli from the SART) underlying specific cognitive impairment in patients with SCH compared with HC participants and 2) apply dynamic network analysis to explore whether these patterns of network connectivity evolve over time and differ in patients with SCH.

METHODS AND MATERIALS

The current study was approved by the Shaar Menashe Mental Health Center institutional ethics review committee. Participants received the equivalent of $25 (U.S.) reimbursement for participation.

Subjects

A total of 25 in-unit patients with SCH at Shaar Menashe Mental Health Center meeting the criteria for DSM-IV-TR schizophrenia (37) were recruited. Patients with SCH with a history of neurology disorders, comorbidity, and drug abuse were excluded from the study. Of the sample, 2 SCH datasets were excluded due to the participants' inability to understand the task requirements, and another 2 datasets were excluded due to excessive head movement. As such, 21 SCH datasets were analyzed. A trained psychiatrist administered the Scale for the Assessment of Positive Symptoms (38) and the Scale for the Assessment of Negative Symptoms (39) to assess clinical symptoms of SCH and administered the Neurological Evaluation Scale (40) to index soft neurological signs.

A total of 30 HC participants without any previous or current history of psychiatric illness, or alcohol/drug dependence or abuse or head injury, were recruited through local advertisements. Of the sample, 2 HC datasets were excluded due to preexisting psychiatric conditions. As such, 28 HC datasets were analyzed.

All participants completed a general demographic questionnaire (Table 1).

Experimental Design

Participants had the BioSemi head-cap (BioSemi, Amsterdam, The Netherlands) consisting of 64 EEG sensors (10/20 international system) placed on their head. EEG signals were recorded by the BioSemi ActiveTwo EEG measurement system using Ag-AgCl active electrodes. EEG signals were digitized online at a sampling rate of 1024 Hz. Once the EEG was set up, participants completed the computerized SART (see the Supplement) (30) using E-Prime version 2 technology (Psychology Software Tools, Pittsburgh, PA), which sent triggers to the BioSemi system via a USB relay (KMTronic USB

Table 1. Demographic, Clinical, and Behavioral Data (Performance on the SART) for Patients With Schizophrenia and Healthy Control Participants

	Patients With Schizophrenia[a] (n = 21)	Healthy Control Participants (n = 28)	p Value
Age, Years	38 ± 12	34 ± 10	.244
Gender (Male:Female)	14:7	18:10	.862
Education, Years	13 ± 1	15 ± 1	.001[b]
Handedness (Right:Left)	20:1	27:1	.835
Duration of Illness, Years	12 ± 7	NA	NA
Hospitalizations	9 ± 9	NA	NA
SAPS Total	35 ± 16	NA	NA
SANS Total	82 ± 18	NA	NA
SANS Attention Subscale	8 ± 2	NA	NA
NES Total	2 ± 1	NA	NA
SART RT	475 ± 74	379 ± 44	< .001[b]
SART Intravariability	0.26 ± 0.07	0.18 ± 0.05	< .001[b]
SART Omission Errors	16 ± 18	0 ± 2	.001[b]
SART Commission Errors	9 ± 8	6 ± 4	< .001[b]

Data are mean ± SD or n.

NA, not applicable; NES, Neurological Evaluation Scale; RT, reaction time; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SART, Sustained Attention to Response Task.

[a]Medication: in patients with schizophrenia, 38% received atypical antipsychotics (olanzapine or risperidone) and 62% received typical antipsychotics (zuclopenthixol depot injections, haloperidol, perphenazine, or levomepromazine).

[b]$p < .01$.