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Relationship between MEG global dynamic functional network connectivity measures and symptoms in schizophrenia

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ABSTRACT

An investigation of differences in dynamic functional network connectivity (dFNC) of healthy controls (HC) versus that of schizophrenia patients (SP) was completed, using eyes-open resting state MEG data. The MEG analysis utilized a source-space activity estimate (MNE/dSPM) whose result was the input to a group spatial independent component analysis (ICA), on which the networks of our MEG dFNC analysis were based. We have previously reported that our MEG dFNC revealed that SP change between brain meta-states (repeating patterns of network correlations which are allowed to overlap in time) significantly more often and to states which are more different, relative to HC. Here, we extend our previous work to investigate the relationship between symptomology in SP and four meta-state metrics. We found a significant correlation between positive symptoms and the two meta-state metrics which showed significant differences between HC and SP. These two statistics quantified 1) how often individuals change state and 2) the total distance traveled within the state-space. We additionally found that a clustering of the meta-state metrics divides SP into groups which vary in symptomology. These results indicate specific relationships between symptomology and brain function for SP.

1. Introduction

Numerous psychiatric disorders, including schizophrenia, have low treatment success rates and create a diminished quality of life for those that suffer. Schizophrenia is a debilitating mental disorder whose treatment has changed little in decades. Successful treatment is often focused on symptom reduction yet many individuals continue to have deeply unsatisfying day-to-day functioning. It is imperative therefore that research capitalize upon newer techniques and analysis methods that can aid in informing: identification and classification, such as patients with co-morbidities; new treatment targets; and illness trajectory. We show here how dynamic functional network connectivity (dFNC) utilizing MEG data may provide unique information that moves us toward a better understanding of the relationship between brain states, how individuals move through these states, and symptoms in SP.

Functional network connectivity (FNC) is defined as the way in which sets of brain areas (or networks) work together over time, represented by statistical associations between the networks where the spatial proximity of the regions to one another may not be an important factor. Since an increasing body of literature suggests that neural oscillations perform a key role in binding separate brain regions together and promoting information transfer between distant brain areas (Buzsaki and Draguhn, 2004; Engel and Singer, 2001; Roopun et al., 2008) FNC has become an important metric for the study of how this process naturally occurs (Allen et al., 2014; Calhoun et al., 2014; Jafri et al., 2008). Furthermore, appropriate connectivity between brain regions is now generally accepted as being key to healthy brain function (Hall et al., 2014). Clearly the temporal as well as the spatial properties of these networks is important to our understanding of brain function, and it is probable that the definition of a network may vary on different time scales (Erhardt et al., 2011). FNC has often been investigated within the resting state (i.e., in the absence of a defined task) using fMRI (Allen et al., 2011; Biswal et al., 1995; Biswal, 2012) and, to a lesser extent the electrophysiological methods MEG and EEG (Allen et al., 2017; Brookes et al., 2011; Meier et al., 2016; Nugent et al., 2017), in diverse populations including schizophrenia, depression, bipolar disorder, and in aging (Alamian et al., 2017; Cetin et al., 2016; Dong et al., 2017, 2018; Du et al., 2016; Fox et al., 2017; Houck et al., 2017; Madden et al., 2017; Nashiro et al. 201;7; Roiser et al., 2013; Wu et al., 2017). However, the timescale of an FNC map (the scan length) is somewhat arbitrary, and there is evidence that important information is being "diluted" with the use of FNC maps that condense several minutes of measurement into a single statistical map. This is particularly a problem for electrophysiological data where there is evidence of brain-state changes on the order of hundreds of milliseconds (Vidaurre et al., 2016).

A logical extension of FNC that looks at how states vary over small time "windows" in order to capture networks on a finer temporal

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scale, has been termed dynamic functional network connectivity (dFNC). dFNC is defined as the (Gaussian tapered) windowed zero-lag cross-correlations among networks. Much previous work has found that these sets of correlations can be grouped into stable repeating patterns of activity representing a few often-visited brain states that may be identified using a k-means clustering of the correlation patterns at each time-point (cluster states [Allen et al., 2011; Miller et al., 2014, 2016]). dFNC has also been investigated in resting state fMRI (Miller et al., 2016; Sakoglu et al., 2010) and in diagnostic groups such as schizophrenia patients (Damaraju et al., 2014; Du et al., 2016; Miller et al., 2016), where for schizophrenia patients in an eyes-closed resting scan it has been shown that there is a reduction in fluidity, or dynamism, in their ability to move from state to state. Importantly, the dFNC spatial patterns of intra-subject dynamic variability have been shown to largely overlap with that of inter-subject variability, both of which were highly reproducible across repeated scanning sessions (Abrol et al., 2016). dFNC has therefore been established as a useful tool for both investigating changing brain states as well as for determining how these states vary between patient populations. The metrics (e.g. meta-state metrics) derived from these repeating connectivity patterns can then be used to further investigate population differences. We here determined the relationship between meta-state metrics and symptomology in SP. We hypothesized that the meta-state metrics where we found significant differences between HC and SP groups in our previous study (Sanfratello et al., 2019) would correlate with symptoms for SP. These metrics measured how often SP changed between brain states and how different the next brain state was from the previous one occupied (Table 1). We also completed a preliminary investigation of whether global-level metrics would group SP in a data-driven fashion, where the number of groups was not specified a priori.

2. Methods

2.1. Participants

Briefly, this investigation utilized existing data (Aine et al., 2017) from 36 schizophrenia patients from whom informed consent was obtained according to institutional guidelines at the University of New Mexico Human Research Protections Office (HRPO). Note that these were the same individuals used for the analysis presented in Table 1 (Sanfratello et al., 2019). There was no significant difference in age or gender between the HC (Mean Age ± SD = 35.7 ± 11.8; 27 M/9F) and SP (Mean Age ± SD = 38.4 ± 13.5; 31 M/5F) groups and all participants were right handed. All participants were compensated for their participation. Patients with a diagnosis of schizophrenia or schizoaffective disorder were invited to participate. Each patient completed the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1997) for diagnostic confirmation and evaluation of comorbidities. Exclusion criteria included history of neurological disorders, mental retardation, substance abuse, or clinical instability. Patients were treated with a variety of antipsychotic medications, therefore doses of antipsychotic medications were converted to olanzapine equivalents (Gardner et al., 2010). Each participant completed resting MEG and structural MRI scans; some also completed additional task and resting fMRI scans as part of a larger study. All patients also completed the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) interview. Positive symptoms include: delusions, conceptual disorganization, hallucinations, excitement, grandiosity, suspiciousness/persecution, hostility; negative symptoms include: blunted affect, emotional withdrawal, poor rapport, passivity, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking. Mean PANSS scores for SP were (Total = 30.3 ± 6.6; Positive = 15.2 ± 5.0; Negative = 15.1 ± 5.6). The participant data and preprocessing used for this study overlapped with that presented in (Houck et al., 2017; Sanfratello et al., 2019) but the analytic approach developed in this work and the questions being investigated are novel and distinct.

Table 1
HC (N = 36) and SP (N = 36) groups reveal significant differences in how often they change between brain states ("Change between states") and in how different the previous brain state is from the next one occupied ("Total distance traveled through state space"). Significant differences between HC and SP groups are highlighted ($p < 0.05$).

	Number of states	Change between states	State space span	Total distance traveled through state space
Mean HC	10.11	50.39	5.25	51.53
Mean SP	11.03	58.89	5.56	61.05
T-value	-1.42	-2.15	-1.43	-2.33
p-Value	0.16	**0.035***	0.16	**0.022***

2.2. MEG

The details of the MEG and MRI data acquisition and processing can be found in (Sanfratello et al., 2019) as well as in the supplementary material. Briefly, 5 min of eyes-open resting state MEG data were acquired. The cortical surface of each participant was reconstructed from T1-weighted MRI images. Activity at each vertex of the cortical surface was determined using a noise-normalized minimum norm estimate (MNE/dSPM; Dale et al., 1999). In essence, MNE/dSPM identifies where the estimated current differs significantly from baseline noise (e.g., empty room data); this method also acts to reduce the location bias of the estimates (Gramfort et al., 2014). Spatiotemporal source distribution maps downsampled to a 50 Hz sampling rate were obtained at each time point (providing an upper frequency bound of 25 Hz) for 60 s of the data. Group spatial ICA (gsICA) was applied to the individual subject MNE/dSPM source-space maps using the GIFT toolbox (http://mialab.mrn.org/software/gift) as in our prior work (Houck et al., 2017; Sanfratello et al., 2019) in order both to separate out overlapping sources and to mitigate the signal leakage issue (i.e. the leakage of signal between projected timecourses, or point spread, which manifests as zero-lag correlations between timecourses of spatially separate regions). Spatial maps were generated by decomposing the mixed MEG timecourses to yield a set of 32 spatially independent and temporally coherent networks. The final number of components was selected by determining that 1) networks (single or multiple areas of activation) were not being lost by the reduction in number of components and 2) that the same area was not being "broken up" into numerous components when only a single area of activation was present. This was an important consideration since later analyses involved multiple statistical comparisons. Furthermore, this data should contain a minimum of artifact components (in the present case we found no artifact components) due to noise reduction and artifact removal during preprocessing. The Infomax ICA algorithm was applied 10 times via ICASSO (Himberg et al., 2004). Subject-specific maps and timecourses were estimated using a back-reconstruction approach based on PCA compression and projection (Allen et al., 2011; Calhoun et al., 2001; Erhardt et al., 2011).

2.3. dFNC and k-means clustering of repeating brain states

By definition dFNC is the (Gaussian tapered) windowed zero-lag cross-correlations among brain networks. Due to the frequency content of our data we chose a 4-second window for the dFNC, capturing all available frequencies of interest (1 Hz–25 Hz). Next, a dFNC analysis was conducted between all 32 ICs calculated from the gsICA at each timepoint. The resulting states were then clustered into repeating patterns using the k-means clustering method (Allen et al., 2011; Miller et al., 2016). This resulted in 3 cluster-states (Sanfratello et al., 2019). We summarized the temporal behavior of the resulting cluster states, which are then allowed to overlap in time, into meta-states; that is, a representation of how much a given subject is in each of the cluster states at each point in time. This approach builds distance vectors to the cluster centroids for each windowed FNC matrix. More specifically,

windowed FNCs are modeled as "weighted sums of maximally independent connectivity patterns (CP)". Discretized CP distance vectors are called meta-states. The meta-state metrics calculated in this manner were (Miller et al., 2016): 1) The number of distinct meta-states subjects occupy during the scan length ("Number of states"); 2) The number of times that subjects switch from one meta-state to another ("Change between states"); 3) The range of meta-states subjects occupy, i.e., the largest L1 distance between occupied meta-states ("State span"); and 4) The overall distance traveled by each subject through the state space (the sum of the L1 distances between successive meta-states, ("Total distance"). These meta-state metrics were then investigated for their relationship to symptoms in SP.

2.4. Investigation into the relationship between meta-state statistics and symptomology in SP

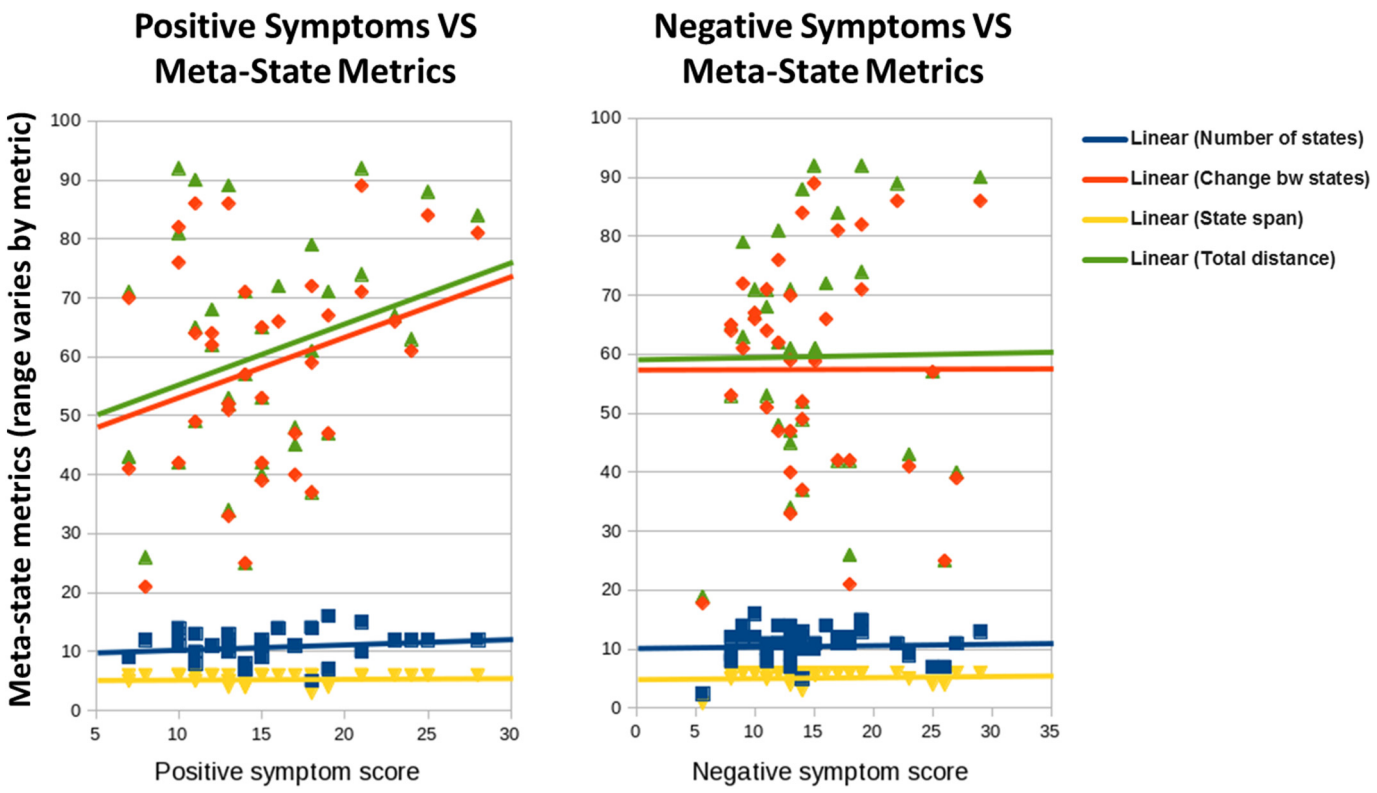
Since we were interested in determining how symptoms are related to how SP traverse brain states we correlated total positive and total negative symptoms with each of the 4 meta-state statistics. In addition, one goal of our work is to develop sensitive tools to classify individuals into appropriate groupings, particularly when individuals have co-morbidities or symptomology that overlap with multiple diagnoses. Therefore, we also investigated if a data-driven k-means clustering of the meta-state level statistics would inform classification of patients.

3. Results

3.1. dFNC meta-state statistics and symptoms in SP

First, we found that positive symptoms significantly correlate with the meta-state metrics "Change between states" and "Total distance" (Fig. 1). No significant correlation between negative symptoms and the various meta-state metrics was found. An investigation into the positive symptom items revealed that only grandiosity correlated with the meta-state statistics.

Second, results from a data-driven k-means cluster analysis based on the global meta-state level metrics revealed a trend for patients to group according to their symptomology. Specifically, the analysis determined that 4 groups was optimal for this dataset (>80% variance explained, Table 2), where it revealed one group that was high in reported positive and negative symptoms (group 2), one group which was relatively high in positive symptoms but low in negative symptoms (group 4), one which was relatively low in positive symptoms but high in negative symptoms (group 1), and one group which was relatively low in both positive and negative symptoms (group 3). We find significant differences in negative symptoms between groups 1 & 4 and 2 & 4, as would be expected if this is to be a useful method for differentiating between patient symptomology. However, we do not find significant differences between any of the groups for positive symptoms for this small set of patients. It is also clear from Table 2 that the 4 groups are significantly different from each other on the meta-state metrics



Correlations				
	Number of States	Change between States	State span	Total Distance
Olanz Equivalent	-0.159	-0.212	-0.072	-0.206
Positive symptoms	0.183	**0.290***	0.078	**0.276***
Negative symptoms	-0.106	-0.107	-0.143	-0.093

Fig. 1. Correlations between global meta-state metrics and symptoms in SP. Blue squares and line = Number of states; Orange diamonds and line = Change between states; yellow down pointing triangles and line = State span; green up pointing triangles and line = Total Distance. Significant correlations ($p < 0.05$) are observed for positive symptoms and meta-state statistics "change between states" and "total distance traveled".

Table 2
Clustering of meta-state statistics splits SP into groupings differentiated by symptomology. Significant differences between groups are highlighted ($p < 0.05$).

	# SP	Gender 0=f; 1=m	Age	Olanzapine equivelant	Total positive	Total negative	Number of states	Change bw states	State span	Total distance
Group 1	9	0.89	33.19	19.82	13.00	18.78	9.89	35.56	5.22	37.11
Group 2	7	0.86	40.38	14.53	16.86	18.29	12.14	83.43	6.00	88.00
Group 3	7	0.86	44.29	12.11	14.57	13.86	10.00	50.86	5.00	51.29
Group 4	13	0.92	37.85	15.05	16.15	11.46	11.77	66.00	5.85	68.38
ttest 1-2		0.8610	0.3720	0.3695	0.2081	0.8628	**0.0449**	**6.59E-010**	0.0828	**1.64E-010**
ttest 1-3		0.8610	0.0654	0.1666	0.3773	0.0900	0.9273	**2.67E-004**	0.6821	**3.56E-004**
ttest 1-4		0.7960	0.4363	0.2698	0.1272	**0.0007**	0.1109	**1.25E-010**	0.0694	**2.12E-010**
ttest 2-3		1.0000	0.6027	0.6122	0.4702	0.1616	0.0554	**2.60E-009**	**0.0213**	**4.87E-010**
ttest 2-4		0.6601	0.7282	0.8970	0.8055	**0.0030**	0.7381	**4.69E-008**	0.2986	**9.08E-008**
ttest 3-4		0.6601	0.2642	0.4116	0.4484	0.2223	0.1616	**1.70E-007**	**0.0129**	**3.97E-007**

"Change between states" and "Total distance", and that in addition groups 1 & 2 are significantly different from each other on the metric "Number of states" and that groups 2 & 3 and groups 3 & 4 are significantly different from each other on the meta-state metric "State span". No significant differences were found between the 4 groups in age, gender, or medication dose, and we found only a small range of symptom scores for this group of SP (Table 3).

4. Discussion

Perhaps the most important message from the current results is that for SP positive symptoms are significantly correlated with how patients are transitioning between brain states (as measured by the pattern of correlations between areas of brain activity). Specifically, the more positive symptoms a patient has the more likely they will be to both change states frequently and to change to states which are more different from the previous state occupied. This may have implications for treatment, especially if these results can be replicated in a larger sample and with patients who have a broader range of symptom scores (see Table 3). The particular relationship we observed, where positive symptoms are positively correlated with how often individuals change states, may have a direct relationship with the well-documented difficulties that SP have with attention (Reichenberg and Harvey, 2007; Bora et al., 2010; Nuechterlein et al., 2015; Hoonakker et al., 2017; Reinhart et al., 2018). For example, in a recent meta-analysis of fMRI connectivity studies of SP (Dong et al., 2018) it was found that a disconnected large-scale brain network model of schizophrenia was supported in which the ventral attention network plays the core role, and its imbalanced communication with other functional networks may underlie the core difficulty of patients to differentiate self-representation (inner world) and environmental salience processing (outside world).

Furthermore, a "proximal salience" model that postulates that inappropriately assigned salience leads not only to the perceptual and cognitive distortions of acute psychosis but also, via disrupted information processing, to the symptoms of disorganization has been supported by recent studies (Manoliu et al., 2014; Moran et al., 2013; Palaniyappan et al., 2013). This model extends the concept of aberrant salience in schizophrenia to account for disruption to cognition and volition and also links aberrant salience to the long-standing concept of schizophrenia as a disconnection syndrome (Liddle et al., 2016). The current study should therefore be followed up with an investigation into the relationship between the meta-state metrics and an attention measure (e.g. PANSS general scales attention item). We also note the possibility that what these findings indicate could potentially contribute to a disjointed and fragmented sense of reality, however our follow-up analysis did not indicate a significant correlation between "disorganization" and any of the meta-state statistics. Therefore it may be a more general relationship among a combination of positive symptoms that is related to the current results. Furthermore, it appears likely from our results here, combined with our previous work [34] that the way individuals travel through brain states may be considered on a continuum with HC toward one extreme, where transitions are smooth and occur at some optimum frequency, and SP spreading toward the other end of the spectrum as their positive symptoms increase, where transitions become frequent and abrupt (Table 1 & Fig. 1).

Our additional preliminary results, in which we find a trend in a data-driven k-means clustering based on meta-state statistics toward groupings reflective of symptomology, provide additional evidence that the metrics "Change between states" and "Total distance" are related to symptomology for SP. These two statistics appear to be the primary drivers of the clustering, as inferred from these statistics being the only ones which are significantly different between all 4 of the cluster groupings. This result is also of interest as potentially identifying a method of sensitively classifying individuals who have symptomology which overlaps disorder categories (e.g. SP and bipolar patients). However, we clearly need a larger sample size to verify these preliminary results.

Future work will investigate a larger group of patients, with a broader range of frequencies (i.e., including gamma band), and a longer scan duration. With a larger group of individuals we anticipate a definitive answer to the utility of our clustering approach based on meta-state metrics as a method of classifying patients. Higher frequencies and a longer scan duration may affect how many and what brain states are identified and how they vary over time. However, we would argue that scan duration should not dramatically affect the number of states, since only 3 states were identified in the current work. It is probable that the frequency of the neuronal oscillations will form different correlation patterns, which work together but are related in a complex manner. It is unknown at this time if this would affect the global meta-state level metrics, and this is an important open question. As a simple example, we see clear differences in connectivity patterns between fMRI and MEG resting state data of the same individuals, where for example we find highly correlated frontal connections in MEG data which are not observed in the dFNC of fMRI data (Sanfratello et al., 2019). Recall, it is the highly connected MEG dFNC state where we observed differences between HC and SP in (Sanfratello et al., 2019), lending support to the disconnectivity hypothesis of schizophrenia. Furthermore, there is ample evidence that when individual frequency bands are investigated different FNC patterns emerge (Brookes et al., 2011). Lastly, we reiterate the importance of replicating these results with patients who have a broader range of symptoms, since there is no a priori reason to conclude that the results here will remain linear at the extreme.

Table 3
Participant demographics: age, olanzapine equivalent, PANSS total positive symptom score, PANSS total negative symptom score.

	Age	Olanzapine equivalent	Total positive	Total negative
Mean ± SD	38.43	15.57	15.19	15.08
S.D.	13.54	9.33	5.04	5.61
Range	20.0–63.3	2.5–50.0	7.0–28.0	8.0–29.0

Conflict of interest

The authors declare that they have no conflicts of interest.

Contributors

Author L. Sanfratello conducted analyses, literature search, and wrote the first draft of the manuscript. Author J. Houck collected data, conducted analyses, and contributed to and edited drafts of the manuscript. Author V. Calhoun provided guidance, contributed to and edited drafts of the manuscript. All authors have contributed to and approve the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.05.007.

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