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Reduced Parietal Alpha Power and Psychotic Symptoms: Test-Retest Reliability of Resting-State Magnetoencephalography in Schizophrenia and Healthy Controls

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Abstract

Background: Despite increased reporting of resting-state magnetoencephalography (MEG), reliability of those measures remains scarce and predominately reported in healthy controls (HC). As such, there is limited knowledge on MEG resting-state reliability in schizophrenia (SZ).

Methods: To address test-retest reliability in psychosis, a reproducibility study of 26 participants (13-SZ, 13-HC) was performed. We collected eyes open and eyes closed resting-state data during 4 separate instances (2 Visits, 2 runs per visit) to estimate spectral power reliability (power, normalized power, alpha reactivity) across one hour and one week. Intraclass correlation coefficients (ICCs) were calculated. For source modeling, we applied an anatomically constrained linear estimation inverse model known as dynamic statistical parametric mapping (MNE dSPM) and source-based connectivity using the weighted phase lag index.

Results: Across one week there was excellent test-retest reliability in global spectral measures in theta-gamma bands (HC $ICC_{Avg}=0.87$, SZ $ICC_{Avg}=0.87$), regional spectral measures in all bands (HC $ICC_{Avg}=0.86$, SZ $ICC_{Avg}=0.80$), and parietal alpha measures (HC $ICC_{Avg}=0.90$, SZ $ICC_{Avg}=0.84$). Conversely, functional connectivity had poor reliability, as did source spectral power across one hour for SZ. Relative to HC, SZ also had reduced parietal alpha normalized power during eyes closed only, reduced alpha reactivity, and an association between higher PANSS positive scores and lower parietal alpha power.

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Conflict of Interest

All authors declare they have no potential conflicts of interest in relation to the work described.

Conclusions: There was excellent to good test-retest reliability in most MEG spectral measures with a few exceptions in the schizophrenia patient group. Overall, these findings encourage the use of resting-state MEG while emphasizing the importance of determining reliability in clinical populations.

Keywords

Schizophrenia; MEG; test-retest reliability; resting-state; spectral power; symptoms

1. Introduction

Spontaneous neural oscillations during a resting-state have been used to study abnormal neurophysiology in a variety of clinical disorders. MEG spectral power measures have been informative in schizophrenia (Canive et al., 1996; Fehr et al., 2001; Rutter et al., 2009; Sperling et al., 2002; Zeev-Wolf et al., 2018) and Alzheimer's disease (Poza et al., 2007; Verdoorn et al., 2011), while MEG functional connectivity has revealed patient abnormalities in schizophrenia (Houck et al., 2017; Sanfratello et al., 2019), mild cognitive impairment (Dimitriadis et al., 2018), and depression (Nugent et al., 2015). Assessing MEG-derived neural oscillations in clinical populations has the potential to yield biomarkers for early detection and diagnosis (Sun et al., 2013; Tan et al., 2015; Uhlhaas et al., 2017); therefore, demonstrating the reliability of MEG resting-state spectral power and functional connectivity in patients is critical. In HC, MEG spectral power in sensor and source space has good reliability in the theta, alpha, and beta bands ($ICCs > 0.6$) over a 7 day test-retest interval, with lower reliability in delta and gamma bands in an eyes open resting-state (Martin-Buro et al., 2016). Reliability of MEG functional connectivity in HC has varied depending on connectivity measure, with good reliability of phase-locking values in alpha, beta, and gamma bands ($ICCs > 0.74$) but poor reliability for phase-lag index across all frequencies ($ICCs < 0.1$) over a 7 day test-retest interval (Garces et al., 2016). Reliability still needs to be quantified for other dependent variables, analysis methods and patient populations; thus far, the reliability of resting-state oscillatory measures in patients with schizophrenia remains unknown.

Schizophrenia has been conceptualized as a disorder of altered brain connectivity or “disconnectivity” (Friston, 1998) based on disruptions in resting-state brain networks highlighting disorganization as a key process (Friston et al., 2016). There have been several MEG studies reporting disrupted neural oscillations and brain connectivity within either an eyes open (EO) or eyes closed (EC) resting-state in schizophrenia (Canive et al., 1996; Chen et al., 2016; Fehr et al., 2001; Fehr et al., 2003; Hinkley et al., 2010; Hinkley et al., 2011; Houck et al., 2017; Rutter et al., 2009; Sanfratello et al., 2019; Zeev-Wolf et al., 2018), for review refer to (Alamian et al., 2017; Hinkley et al., 2010; Siekmeier and Stufflebeam, 2010). Study results indicate that patients had increased slow-wave oscillatory activity within delta and theta frequencies (Chen et al., 2016; Fehr et al., 2001), decreased gamma oscillatory activity (Rutter et al., 2009), and decreased alpha oscillatory activity in widespread regions during EC (Canive et al., 1998; Canive et al., 1996) and EO (Zeev-Wolf et al., 2018) resting-states, along with reduced alpha-band connectivity in left prefrontal cortex and right superior temporal cortex (Hinkley et al., 2011), with clinical correlates

ranging from associations with positive symptoms (Hinkley et al., 2011; Kim et al., 2014; Zeev-Wolf et al., 2018) to negative symptoms (Chen et al., 2016; Fehr et al., 2003; Hinkley et al., 2011; Zeev-Wolf et al., 2018) depending on frequency band and brain region. Inconsistencies in cross-sectional literature may be attributed to variations in rest collected (EO vs EC), analysis method, measure used, and frequency band.

Narrowing the field on potential biomarkers for schizophrenia will require the reproducibility and reliability of previous findings before embarking on longitudinal studies. It is critical for MEG research to complete its own test-retest studies, as reliability may be influenced by modality, type of data (evoked vs. spontaneous), analysis method, and/or imaging site. Despite the same temporal resolution capabilities for EEG and MEG, MEG provides a number of advantages. For EEG, the poor conductivity of the skull creates a smearing effect such that the brain signals picked up by the electrodes are not necessarily from local generators. MEG offers a reference-free method for assessing electromagnetic signals which are not distorted by the differing conductivities of the scalp, skull, and brain, thereby allowing for improved spatial resolution and the application of simpler models for estimating sources of measured activity.

The current study was designed to examine global and regional test-retest reliability of neuromagnetic oscillatory measures across sensor and source MEG data in EC and EO resting-states. We collected resting-state data in 26 participants (13-SZ, 13-HC) during 2 visits to estimate reliability across one hour and one week in spectral power measures and functional connectivity. We hypothesized test-retest reliability would be moderately high in HC and lower in SZ. Alpha oscillatory activity in the parietal region was also examined based on its well-defined physiological properties, that is, the known suppression of response amplitude to eye opening in the parietal-occipital regions. Given that we collected both EC and EO data, we directly examined alpha reactivity. We hypothesized resting-state alpha oscillatory activity would be decreased in SZ when compared to HC, similar to previous MEG studies (Canive et al., 1998; Canive et al., 1996; Zeev-Wolf et al., 2018), partially attributed to potential thalamic abnormalities and thalamic connectivity aberrations previously reported in SZ (Cetin et al., 2014; Sponheim et al., 2000; Uhlhaas et al., 2008), and the thalamus' role in generating oscillatory activity in the parietal-occipital regions.

2. Materials and Methods

2.1 Participants

The current study included 13 individuals diagnosed with schizophrenia (SZ) and 13 healthy controls (HC), age and gender matched, Table 1. Informed consent was obtained from all participants according to institutional guidelines. The study was approved by the University of New Mexico Health Sciences Center Human Research Review Committee. All participants were within 21–49 years of age with no history of neurological disorder (e.g. epilepsy), no history of major head trauma (loss of consciousness >5 min), no current substance abuse diagnosis (excluding nicotine), no current dependence/abuse of PCP/ amphetamine/cocaine within the past 12 months, and were not currently on mood stabilizers such as lithium or valproic acid. HC had IQ scores within the normal range and no history of developmental delays or neurological or psychiatric disorders based on the Structured

Clinical Interview for DSM-IV-Non-patient (SCIDNP). HCs also did not have a family history of a psychotic disorder in first-degree relatives or a history of more than 1 lifetime depressive episode. Participants with schizophrenia were confirmed to have a DSM-IV-TR diagnosis of schizophrenia with the Structured Clinical Interview for DSM-IV-Patient (SCID-IP) and retrospective clinical stability. Participants were not excluded for nicotine use, however, they were not allowed to smoke within 1 hour of the MEG session or be more than 5 hours from their previous cigarette to avoid confounds of acute nicotine exposure or withdrawal. The following assessments were collected in SZ participants and reported in Table 1: Wechsler Test of Adult Reading (WTAR), Standard and Predicted (premorbid) IQ, Positive and Negative Syndrome Scale (PANSS), antipsychotic medication dose information, and duration of illness. PANSS scores were determined for each visit. Antipsychotic medication was converted to olanzapine equivalents for comparison between medication (Gardner et al., 2010). Duration of illness was calculated by subtracting age at onset of psychotic symptoms from current age.

2.2 MEG Behavioral Tasks

All participants had two visits across 7 days [HC=7.54 days $\pm$ 60 minutes, SZ=7.84 days $\pm$ 51 minutes]. Time of day between visits was matched to take into account circadian rhythm. Each visit began with a 10-minute rest task (referred to as Rest10) and ended with a 4-minute rest task (referred to as Rest4), see Figure 1. No responses were required from the participant; however, participants were instructed to attend the instructions for prompts to close their eyes or fixate on a white cross. Each task alternated between EC and EO. In total, resting-state activity was recorded 4 separate times with 14 minutes of EO and 14 minutes of EC.

2.3.1 MEG Data Acquisition—MEG data were collected in a magnetically shielded room (Vacuumschmelze – Ak3B) at the Mind Research Network in Albuquerque, New Mexico using a 306-channel whole-head MEG system (Elekta Neuromag) with a sampling rate of 1000 Hz and an antialiasing filter with a passband of 0.1–330 Hz. Prior to data acquisition, four electromagnetic coils were placed on the participant's mastoid bone and upper forehead, along with electro-oculogram and electrocardiogram channels. The location of the coils were registered to the nasion and preauricular points using three-dimensional digitization equipment (Polhemus FastTrack). Participants sat upright in the MEG during the task. Continuous Head Position Indicator (cHPI) monitoring allowed for motion correction. Head position was checked between visits. For the Rest10 task, average Euclidean distance between visits was 4.62 mm for HC and 6.06 mm for SZ. For the Rest4 task, the distance was 4.90 mm for HC and 6.12 mm for SZ. Head position consistency was similar between HC and SZ (all p 's > 0.31).

2.3.2 Structural MRI Data Acquisition—Structural MRIs were obtained for mapping source locations. Sagittal T1-weighted anatomical MR images were obtained using a Siemens TIM Trio 3 Tesla MRI system with a 32-channel head coil. Parameters of the multiecho 3D MPRAGE sequence were: TR/TE/TI = 2530/1.64, 3.5, 5.36, 7.22, 9.08/1200 ms, flip angle = 7°, field of view (FOV) = 256 mm x 256 mm, matrix = 256 × 256, 1 mm thick slice, 192 slices, GRAPPA acceleration = 2.

2.4 MEG Data Preprocessing

Raw MEG data were filtered for noise and corrected for head motion with the Neuromag Max-Filter 2.2 software using the temporal extension of signal space separation (t-SSS) method with movement compensation (Taulu and Hari, 2009; Taulu and Kajola, 2005). MEG data from each subject's Visit 2 was transformed to Visit 1 head position using Maxfilter 2.2 MaxMove option to ensure equivalent sensor locations between visits. No downsampling of the data was implemented at the preprocessing stage. Heartbeat and eye-blink artifacts were automatically detected and removed using signal space projection (SSP) (Uusitalo and Ilmoniemi, 1997) in MNE software (Gramfort et al., 2013). The continuous data were segmented into artifact-free 2 second epochs. Epochs in which the magnetic field exceeded 5 pT were rejected. HC had 2.4% and SZ had 4.6% of all epochs rejected. The total number of epochs used for further analysis included 401 EC, 402 EO epochs in HC, and 393 EC, 403 EO epochs in SZ. The number of closed/open epochs did not differ between groups (all p 's > 0.25).

2.5 MEG Spectral Analyses

For sensor analysis, we applied the summary spectral measures described in Poza et al. (2007) to simplify multi-channel MEG spectral data. Using only planar gradiometers, the sensor array was divided into left and right equivalent regions, see Figure 2. Spectral power was estimated using Matlab's FFT function with a window size of 2048 for the following frequency bands: Delta (1–4 Hz), Theta (5–8 Hz), Alpha (9–13 Hz), Beta (14–29 Hz), and Gamma (31–58 Hz). Spectral measures included: power, normalized power, half-power, Shannon Spectral Entropy (SSE), and alpha reactivity. Normalized power was obtained by dividing the power within the frequency band by total 1–50 Hz power. Half power was defined as the midpoint frequency where half of the power is below/above for the 1–50 Hz range and indicates overall spectral power shifts from low to high frequencies. Alpha reactivity was calculated using normalized spectral power values with the following: (EC-EO)/EO. Global measures were the average of all regions and gradiometers.

For source analysis, the cortical surface of each participant was reconstructed from T1-weighted MRI files using FreeSurfer with a repeatedly subdivided octahedron as the spatial subsampling method, creating 4,098 locations per hemisphere with a source space of 4.9 mm. Source analysis was performed with MNE software (Gramfort et al., 2013; Gramfort et al., 2014) using an anatomically constrained linear estimation inverse model known as dynamic statistical parametric mapping (dSPM) (Dale et al., 2000). The regularization parameter corresponded with a signal-to-noise ratio of 3. Source orientation had a loose constraint of 0.2. The forward solution was calculated with a single layer (inner skull) boundary element method. The dSPM inverse model identified where the estimated current at each cortical surface vertex differed significantly from baseline noise (empty room data). Power spectral density (PSD) measures were computed from epochs using a multi-taper method with Discrete Prolate Spheroidal Sequence (DPSS) windows for each frequency band and region, using 7 tapers at 4 Hz and regions of interest based on the FreeSurfer DKT atlas (Desikan et al., 2006; Klein and Tourville, 2012). PSD represents the average spectral power derived from each voxel time series for each regional label. Global measures were data from all regional labels averaged. Normalized power was obtained by dividing the

power within frequency band by the total 1–58 Hz power. Functional network connectivity was estimated using a debiased estimator of the squared weighted phase lag index (wPLI-debiased) (Vinck et al., 2011). The FNC measure, wPLI-debiased, detects true changes in phase-synchronization, while reducing the influence of common noise sources, changes in phase of coherency, and avoids spuriously increases by volume-conduction. It estimates the extent of observed phase leads and lags by the magnitude of the imaginary component of the cross-spectrum (Vinck et al., 2011). All data were exported to MATLAB (2018a, MathWorks) and run through custom scripts.

2.6 Intraclass Correlation (ICC)

ICC estimates and their 95% confidence intervals were calculated in SPSS to assess the between and within-subject variability using a two-way mixed effects model with absolute agreement, single measurement criteria, also known as ICC (3,1) model (McGraw and Wong, 1996; Shrout and Fleiss, 1979). ICCs were calculated for multiple rest iterations: for each visit (across one hour), for each task (across one week) and for all runs. ICCs ranged from 0 to 1 (negative values scored as zero) with higher values indicating better reliability. Following the guidelines of (Cicchetti and Sparrow, 1981) we defined ICCs as: excellent reliability >0.75 , good reliability $0.75-0.60$, fair reliability $0.59-0.40$, and poor reliability <0.40 .

2.7 Statistical Analysis

All statistics were performed using SPSS (version 25 for Macintosh). Mixed Effect Repeated Measures-Analysis of Variance (RM-ANOVAs) had statistical thresholds set at $p<0.05$. Greenhouse-Geisser corrections were made for sphericity violations. The between-subject factor was Group (HC,SZ), within-subject factors included Hemisphere (Left, Right), Resting-State (EO, EC), and/or Region [Superior Parietal (SupPar), Inferior Parietal (InfPar), Precuneus] depending on measure explored. Significant interactions were followed-up with separate one-way ANOVAs, or t-tests on the factors of interest with familywise multiple comparisons correction using false discovery rate (FDR) correction with $q=0.05$ (Benjamini and Hochberg, 1995).

3. Results

3.1 Reliability of Global Spectral Measures

Global MEG spectral measures had good to excellent test-retest reliability in each frequency band, resting-state and participant group at the sensor and source level, Figure 3 and supplementary Table S1. To summarize the group means reported in Figure 3, per condition group averages are reported below for descriptive purposes. HC had excellent reliability across one hour in all frequency bands ($ICC_{Avg}=0.89$) and across one week in theta-gamma bands ($ICC_{Avg}=0.87$) with the exception of good reliability in delta band across one week ($ICC_{Avg}=0.67$). SZ also had excellent reliability across one hour ($ICC_{Avg}=0.88$) and across one week ($ICC_{Avg}=0.87$) in theta-gamma bands, with exceptions of good reliability in delta band across one hour (Source $ICC_{Avg}=0.69$) and across one week ($ICC_{Avg}=0.74$). Both resting-states had similar reliability levels in HC (Closed $ICC_{Avg}=0.86$, Open $ICC_{Avg}=0.87$); however, for SZ the EC average was higher than EO average group mean (Closed

ICC_{Avg}=0.89, Open ICC_{Avg}=0.83). Between condition group averages were not tested further.

3.2 Reliability of Regional Spectral Measures

Regional ICC estimates from the Rest10 task were calculated for normalized power across one week, Figure 4. HC had excellent Rest10 task reliability across a week in most sensor regions and bands (ICC_{Avg}=0.86), with an exception of delta, right orbital region during EC (ICC=0.46). SZ had excellent Rest10 task reliability in many bands and regions (ICC_{Avg}=0.80), with the lowest reliability in delta and theta bands during EO (delta ICC_{Avg}=0.73, theta ICC_{Avg}=0.69) and lower reliability than HC in several regions.

Parietal region ICC estimates within the alpha frequency band are shown in Figure 5 and supplementary Table S2. HC had excellent reliability for the parietal alpha spectral measures (power, normalized power, half power, SSE) across one hour (ICC_{Avg}=0.93) and across one week (ICC_{Avg}=0.90) with the exception of good reliability in alpha reactivity (ICC_{Avg}=0.67). SZ had excellent reliability for most parietal alpha measures across one hour (ICC_{Avg}=0.80) and across one week (ICC_{Avg}=0.84), with the exceptions of good reliability of alpha reactivity (ICC_{Avg}=0.64) and poor reliability in source power across one hour (ICC_{Avg}=0.05). Both resting-states had similar reliability levels in HC (Closed ICC_{Avg}=0.92 vs. Open ICC_{Avg}=0.90) and SZ (Closed ICC_{Avg}=0.82 vs. Open ICC_{Avg}=0.82). Source ICCs were generally lower than sensor ICCs.

3.3 Group Differences in Parietal Alpha Measures

At the sensor level, in the EC state only, SZ had reduced parietal normalized power [Figure 6A–6B; State x Group interaction: $F(1,24)=7.73$, $p=.012$; Group effect at EC: $F(1,24)=6.39$, $p=.018$], reduced absolute power [data not shown; State x Group interaction: $F(1,24)=7.37$, $p=.010$; Group effect at EC: $F(1,24)=6.39$, $p=.018$] and reduced alpha reactivity [Figure 6C; Group effect: $F(1,24)=6.16$, $p=.020$]. These reductions in spectral power and normalized power in the EC resting-state, along with reduced alpha reactivity, remained consistent across runs and visits in SZ.

At the source level, SZ had reduced normalized power during EC in several parietal regions [Figure 6D–6E; Group effect at SupPar: $F(1,24)=5.35$, $p=.030$, InfPar: $F(1,24)=6.69$, $p=.016$, and Precuneus: $F(1,24)=5.32$, $p=.030$], along with reduced alpha reactivity [Figure 6F; Group effect: $F(1,24)=12.387$, $p=.002$]. Importantly, group effects in the individual parietal regions (SupPar, InfPar, Precuneus) remained significant following FDR correction for multiple comparisons. There were no interactions or main effects for power at the source level. Overall, parietal source normalized power measures paralleled sensor measures with reductions in SZ during the EC resting-state.

3.4 Source Functional Connectivity

Given that sensor and source analyses revealed group differences in the EC resting-state, we focused connectivity analyses on EC and selected superior parietal regions to parallel our focus on parietal alpha spectral power. For short- and long-range connectivity we selected Superior Parietal to Lateral Occipital and Entorhinal regions. All intervals tested in both

groups had poor test-retest reliability [HC $ICC_{Avg}=0.12$, SZ $ICC_{Avg}=0.03$], Supplementary Table S2. RM-ANOVAs were conducted on connectivity pairs with Run (Visit/Task) as the within-subject factor. There was higher connectivity in SZ between left hemisphere Superior Parietal to Lateral Occipital regions during the Visit2_Rest10 task only [Figure 7A; Run x Group interaction: $F(2.15,51.56)=3.15$, $p=.04$; Group effect at Run 3 ($p=.007$), all others ($p>0.13$)]. SZ also had higher connectivity between Superior Parietal to Entorhinal regions during the Visit1_Rest10 task only [Figure 7B; Run x Group interaction: $F(2.13,51.16)=3.34$, $p=.041$; Group effect at Run 3 ($p=.029$), all others ($p>0.09$)]. Overall, these results show the wPLI-debiased functional connectivity measure lacked consistent FNC findings per run, along with poor ICC values.

3.5 Correlation of MEG Spectral Measures with PANSS Scores

To determine if resting-state normalized power correlated with symptom measures in SZ, we examined normalized power during the Rest10 task with PANSS scores (Positive, Negative, General Scores) from the same visit. We found a moderate negative correlation between EC normalized power in sensor parietal region and PANSS positive scores, Figure 8. Higher positive symptom scores were related to lower alpha normalized power in the EC resting-state during Visit1 [$r=-0.622$, 95% BCa CI $[-.885, -.106]$, $R^2=0.387$, $p=0.023$] and during Visit2 [$r=-0.606$, 95% BCa CI $[-.870, -.046]$, $R^2=0.368$, $p=0.028$] accounting for 38.7% and 36.8% of the shared variance, Figure 8A and 8B. The Rest4 task had similar findings to the Rest10task, higher positive symptom scores were related to lower alpha normalized power in the EC resting-state, during Visit1 [$r=-0.639$, 95% BCa CI $[-.888, -.246]$, $R^2=0.408$, $p=0.019$] and during Visit2 [$r=-0.582$, 95% BCa CI $[-.890, -.029]$, $R^2=0.339$, $p=0.037$], data not shown.

4. Discussion

We examined the test-retest reliability of sensor and source-based resting-state spectral power oscillations in neuromagnetic data across one week. We found excellent test-retest reliability of most MEG spectral measures, replicating previous research (Martin-Buro et al., 2016) while extending findings to schizophrenia. Our reliability results indicate: 1) Global spectral measures of normalized power showed excellent test-retest reliability in theta-gamma bands and good reliability in delta band in both groups, 2) Regional normalized power across one week showed excellent reliability in both groups but lower reliability in SZ, 3) Parietal alpha spectral measures had excellent reliability across one hour and one week in both groups, but poor reliability in source power across one hour in SZ, and 4) Source functional connectivity had unreliable ICC values suggesting the wPLI-debiased measure may not be optimal for test-retest reliability and may not yield replicable findings in SZ. Our study found reduced normalized power and alpha reactivity in SZ during the EC resting-state which negatively correlated with PANSS positive scores indicating higher PANSS positive scores were related to lower parietal alpha normalized power.

Reductions in resting-state alpha oscillations in SZ have been reported previously in MEG studies during EC (Canive et al., 1998; Canive et al., 1996) and EO (Zeev-Wolf et al., 2018) and with EEG (Boutros et al., 2008; Clementz et al., 1994; Goldstein et al., 2015; Lund et

al., 1995), while the underlying functional significance of these alpha differences is unclear. Patients with schizophrenia may have an intrinsic deficit in the ability to generate alpha band oscillations, as reflected by reduced alpha power at illness onset (Clementz et al., 1994; Goldstein et al., 2015), similar alpha power deficits in unmedicated and medicated patients (Canive et al., 1996) and similar alpha band connectivity disruptions between first episode and chronic durations of illness (Di Lorenzo et al., 2015; Sponheim et al., 1994). In the current study, we found reduced alpha spectral power in SZ at both visits across 7 days, with a high reliability/stability of alpha measures between visits (parietal $ICC_{Avg}=0.84$). There is suggestion the alpha deficit would persist, as EEG alpha spectral power values remained stable over 36 months in adult outpatients diagnosed with schizophrenia (parietal $ICCs=0.46-0.75$) (Jetha et al., 2009) and moderately stable over a 9 month period in schizophrenia, bipolar, and nonpsychiatric patients (Clementz et al., 1994). Although, an EEG study indicated that while SZ may have similar reliability levels as HC, 40% more data may be required to obtain similar levels of artifact-free epochs, if using epoch-rejection to control for artifact contamination (Lund et al., 1995). Given that the thalamus plays an important role in generating alpha oscillatory activity in the parietal-occipital areas, reduced alpha power may arise from thalamic dysfunction or tonically enhanced arousal (Cetin et al., 2014; Sponheim et al., 2000; Uhlhaas et al., 2008). Alternatively, cortical generators from the parieto-occipital sulcus (Hari and Salmelin, 1997), visual cortex (Romei et al., 2010) and/or other visual areas such as the fusiform/lingual gyrus (Grent-'t-Jong et al., 2016), along with local and global neural organization (Alamian et al., 2017) may be altered in SZ. The neural oscillations recorded with MEG may arise from a mixture of generating processes ranging from local circuitry to large-scale networks (Benwell et al., 2019); therefore, it is possible that different generators are involved in abnormal alpha oscillations in patients with SZ. Targeting parietal alpha power with Transcranial Magnetic Stimulation (TMS) represents a novel treatment, especially since EEG research has found improvement in patient positive and general psychotic symptoms and alpha power normalization following TMS treatment (Jin et al., 2012).

To our knowledge, this is the first MEG test-retest study in participants with schizophrenia. While participants with schizophrenia had excellent reliability in many spectral measures, there were a few instances of lower reliability (i.e. source power across one hour and generally lower one week values), as well as larger 95% CI around ICC estimates indicating greater variability between visits. However, it is unclear what factors may be driving lower reliability in patients. In the current study we monitored several variables such as time of day, PANSS scores, and medication, and found no difference between visits. Additionally, to ensure compliance with the test-retest design, we recruited a stable cohort of patients who successfully completed other neuroimaging studies and were familiar with imaging procedures minimizing anxiety or task unfamiliarity confounds. Prior MEG spectral test-retest studies have been performed exclusively in healthy controls. Martin-Buro and colleagues (2016) reported good reliability for power in sensor and source space in the theta, alpha, and beta frequency bands ($ICCs >0.6$), with lower reliability in delta and gamma bands in EO. The current study found similar excellent reliability across one week in most regions and bands in HC ($ICCs >0.72$) with lower reliability in delta band EC ($ICCs >0.46$). These results suggest that delta measurements may be impacted by environmental and

biological noise. While the results between studies are similar, ICC estimates were modeled differently and ICC values will fluctuate based on the model and variance assumptions (Koo and Li, 2016; McGraw and Wong, 1996; Shrout and Fleiss, 1979). Other MEG-derived task specific signals at the sensor and source level have also shown high reliability, particularly, auditory steady-state spectral power [ICCs ~0.61–0.82] and phase coherence [ICCs ~0.86–0.96] (Tan et al., 2015), visually induced gamma band oscillations [average ICC=0.861] (Tan et al., 2016), mismatch negativity amplitude [ICC ~0.81–0.90] and peak latency [ICC ~0.74–0.88] (Recasens and Uhlhaas, 2017), paired-click auditory gating [ICCs >0.80] (Lu et al., 2007), N-back working memory M170 response amplitude [ICCs >0.44] and late positive potential [ICCs > 0.93] (Ahonen et al., 2016).

Here we found that source functional connectivity reliability based on weighted-phase lag index (ICC=0–0.32) was much lower than power spectrum reliability (ICC=0.68–0.95). Weighted-phase lag index was used to minimize the impact of volume conduction and zero-lag synchronization, known problems in MEG connectivity analysis; however, it is now clear phase-related connectivity may be poorly suited for test-retest reliability. Prior studies in HC have shown MEG resting-state functional connectivity reliability depends greatly on the frequency band and connectivity measure used, with greatest reliability of phase-locking values in alpha, beta, and gamma bands (averages 0.74–0.82), and lowest reliability for phase-lag index in all frequency bands (ICCs<0.1) (Colclough et al., 2016; Garces et al., 2016). As suggested by others, connectivity measures should employ correlation between orthogonalized, band-limited, power envelopes (Colclough et al., 2016), and/or longer epochs and recordings (Anderson et al., 2011; Birn et al., 2013; Wens et al., 2014) to increase SNR. While phase-based measures have fair repeatability for group-level inference in large datasets, phase-based measures may be noisier estimates in short or noisy recordings, or in smaller studies. Future studies with a larger sample size may find higher reliability of the wppli-debiased measure than reported here, given our small sample size. Furthermore, it remains unknown if the low reliability is due to the FNC measure itself, or the dynamic nature of the brain. Although the current study had a small sample size, we could examine the impact of recording length on reliability. In the current study the longer task (Rest10 vs. Rest4) did not offer significant improvement in wppli connectivity ICC values [HC ICC_{Avg}=0.28, SZ ICC_{Avg}=0.04 for long task vs. HC ICC_{Avg}=0.02, SZ ICC_{Avg}=0.09 for short task].

Although analyzing data in source space minimizes the known issues to field spread and volume conduction that may be present in sensor data, the current study found generally lower reliability values at the source level. Perhaps the lower source reliability may be a reflection of the methods used to attain MEG source constructions (i.e. differences in anatomical versus functional source constructions, or inverse modeling method with MNE dSPM versus beamformer). While other MEG rest studies have used anatomical boundaries to define source regions (Brookes et al., 2018; Cornew et al., 2012; Hillebrand et al., 2012; Hillebrand et al., 2016; Kitzbichler et al., 2015; Tewarie et al., 2014), grouping time courses based on anatomy may blur functional differences. There have been several recent papers using ICA to define functional regions for connectivity analysis in healthy controls (Brookes et al., 2011; Hyvarinen et al., 2010; Nugent et al., 2017) and patients with schizophrenia (Cetin et al., 2016; Houck et al., 2017), however those reports did not address test-retest

reliability of ICA driven functional connectivity. Static functional connectivity estimates may also have lower reliability as critical information is lost by time-averaging the signal. Dynamic functional connectivity estimates which take into account the rapidly modulating, dynamic nature of brain states (Allen et al., 2014; Brookes et al., 2018; Brookes et al., 2014; de Pasquale et al., 2010; Hutchison et al., 2013; O'Neill et al., 2015) may have better reliability.

The current study has several limitations which warrant caution. First, this was a stable, medicated cohort of patients and as such it is unknown how well the results will generalize to other populations. Additionally, all SZ were on various antipsychotic medications; therefore, it cannot be determined whether the spectral abnormalities found were due to the disorder or driven by medication. Given the small group size (n=13) there was limited statistical power for investigating gender differences, medication, diagnosis effects, and all-to-all functional connectivity. It is important to keep in mind that test-retest ICCs are variance measures that report relative changes within or between subject variance over time. Even low ICCs do not necessarily imply the measure itself is inaccurate, but perhaps a true within-subject change occurred, or the sample was too homogenous. Although we found that ICC group average value was a bit higher for EC relative to EO in SZ, it is important for future studies to directly test if a particular rest condition (EO or EC) creates meaningfully different results. While we controlled for variables such as nicotine and illicit drug use between sessions, general patterns or alterations in sleep, caffeine intake and/or alcohol use were not monitored. Given that lack of sleep, excess caffeine, or alcohol withdrawal may impact frequency specific ratios or spectral power, ideally these would be monitored between sessions in future studies. Also, it remains to be seen if the lower reliability of delta, especially in orbital regions, may be partially attributed to eye movements that were not eye-blinks. Finally, as a test-retest study this is a single imaging site with a single Elekta Neuromag MEG system; therefore, without a larger sample size, validation on multiple MEG systems and/or multiple sites, definitive conclusions on reliability cannot be made.

The search for reliable biomarkers in schizophrenia that provide an objective and quantifiable index of network activity is an important avenue of research. Our contribution advances the understanding of reliability of MEG resting-state data in schizophrenia. While our results represent a preliminary exploration of reliability in this clinical population, these results can be built upon to assess population reliability. This research demonstrates that resting-state information in clinical populations can be informative and that MEG is a beneficial tool to capture neural oscillations with good spatial precision and reliability. Given that theta-gamma frequency bands in both resting-states were stable over sessions for both groups we suggest recording both EO and EC data to better capture the neural dynamics. An important next step is to tease out the factors that drive the decreased reliability in patients and find ways to mitigate the issue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1: Rest Task Design.

Rest10 (a 10-minute task) alternates between 2.5 minutes of eyes closed followed by 2.5 minutes of eyes open fixated on a cross. Rest4 (a 4-minute task) alternates between 2 minutes of eyes closed followed by 2 minutes of eyes open fixated on a cross.

Figure 2: Sensor Spectral Analysis.

To simplify multichannel spectral data, we divided the MEG sensor array into regions with an equivalent number of planar gradiometers. The left and right regions included frontal, central, parietal, occipital, anterior, and posterior temporal cortex. To create regional averages, data from 16 gradiometers were averaged.

Figure 3: Global ICCs.

Global ICC estimates based on normalized power were calculated within each visit and across one week for each task. Data represent mean with 95% confidence interval. Healthy controls had excellent to good reliability across one hour and one week in most bands (Sensor ICCs >0.85, Source ICCs >0.72), with the exception fair reliability across one week in delta (Sensor ICCs >0.55, Source ICCs >0.42). Participants with schizophrenia had excellent to fair reliability across one hour and one week (Sensor ICCs >0.80, Source ICCs

>0.52), with slightly lower one week reliability in delta and theta bands (Sensor ICCs >0.71, Source ICCs >0.48).

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Figure 4: Regional ICCs.

Regional ICC estimates from the Rest10 task were calculated across 1 week. Healthy controls had excellent reliability across a week in most sensor regions and bands (ICCs >0.77), with exceptions in the delta band right orbital region during the eyes closed condition (ICCs >0.46) and right central regions during the eyes open condition (ICCs >0.62). Participants with schizophrenia had good reliability in many bands and regions (ICCs >0.65), with the lowest reliability in theta band during the eyes open condition (ICCs >0.57) and slightly lower reliability overall in several regions when compared to healthy controls.

Figure 5: Parietal Region ICCs.

Parietal region ICC estimates based on normalized power were calculated within each visit and across one week for each task. Data represent mean with 95% confidence interval. Healthy controls had excellent to good parietal region reliability across the spectral measures of power, normalized power, half power, and Shannon spectral entropy (Sensor ICCs >0.82 , Source ICCs >0.68), with the exception of fair reliability in alpha reactivity (Sensor ICCs >0.56 , Source ICCs >0.55). At the sensor level, participants with schizophrenia had excellent parietal region reliability across several spectral measures (Sensor ICCs >0.77), with the exception of good to poor reliability for SSE during Eyes Open (ICC = 0.69) and alpha reactivity (ICC = 0.38). At the source level, there was fair reliability of normalized power (ICCs >0.57), power across one week (ICCs >0.69), and alpha reactivity (ICCs >0.43), but poor reliability of power within one hour (ICCs <0.16).

Figure 6: Parietal Region Spectral Analysis.

Data represent mean ($\pm$ SEM), asterisks denote $p < 0.05$. Patients with schizophrenia had reduced parietal alpha power during the eyes closed resting-state only (A). This reduction in sensor level alpha normalized power (B) and alpha reactivity (C) remained significantly reduced across runs and visits over a week. At the source level, patients with schizophrenia had reduced alpha power in several parietal regions [Superior Parietal (SupPar, SP), Inferior Parietal (InfPar, IP), and Precuneus (PC)] during the eyes closed resting-state only (D). This reduction in source level alpha normalized power (E) and alpha reactivity (F) remained significantly reduced across runs and visits over a week.

Figure 7: Source Functional Connectivity.

Data represent mean ($\pm$ SEM), asterisks denote $p < 0.05$. Connectivity based on the weighted phase lag index measure for select region pairs was evaluated across runs. Patients with schizophrenia had increased connectivity in Superior Parietal to Lateral Occipital regions during the Rest10 task on Visit 2 (A) and in Superior Parietal to Entorhinal regions on Visit 1 (B). However, the increase in connectivity did not persist between runs and was found to vary considerably in magnitude and direction between visits in both healthy controls and patients.

Figure 8: Correlation between MEG alpha power and PANSS scores.

Parietal region spectral analysis revealed patients with schizophrenia had reduced parietal alpha power and normalized power during the eyes closed resting-state compared to healthy controls. The eyes closed normalized power in patients negatively correlated with PANSS positive scores during both Visit 1 (A) and Visit 2 (B), indicating increased positive symptoms scores related to reduced parietal alpha power.

Table 1:**Participant Characteristics**

	Healthy Controls (Mean $\pm$SEM)	Patients with Schizophrenia (Mean $\pm$SEM)
<u>Demographics</u>		
Gender (M/F)	8/5	8/5
Age (Males)	32.65 $\pm$ 3.14	32.98 $\pm$ 2.54
Age (Females)	37.95 $\pm$ 2.91	38.35 $\pm$ 3.57
Education (yrs) **	15.23 $\pm$ 0.59	13.00 $\pm$ 0.39
Ethnicity (% Hisp/NonHisp)	23% / 77%	46% / 54%
<u>Clinical:</u>		
WTAR Standard IQ	107.08 $\pm$ 4.17	99.38 $\pm$ 4.69
Standard Range	(77–123)	(77–124)
WTAR Predicted IQ	106.69 $\pm$ 1.70	103.31 $\pm$ 1.34
Predicted Range	(98–116)	(94–111)
<u>PANSS Scores</u>		
Positive (Visit1)	--	11.38 $\pm$ 1.16
Positive (Visit2)	--	11.38 $\pm$ 1.23
Negative (Visit1)	--	11.85 $\pm$ 0.96
Negative (Visit2)	--	11.92 $\pm$ 1.21
General (Visit1)	--	19.77 $\pm$ 0.86
General (Visit2)	--	18.54 $\pm$ 0.86
<u>Medications</u>		
OLZ(mg/day)	--	16.79 $\pm$ 4.11
Duration of Illness (yrs)	--	15.00 $\pm$ 2.59

Asterisks represent significant differences between groups (** p<0.05).

All other comparisons (p>0.05).