IMAGING COHERENCE IN SCHIZOPHRENIA: A PILOT MEG STUDY

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Abstract

Background: Previous studies examining coherence and connectivity deviations in schizophrenia patients relied on standard coherence measures between recording sites. A coherence-imaging methodology where coherence is assessed within imaged brain structures was developed recently by our group. Magnetoencephalography (MEG) based coherence-imaging is yet to be applied to probing the coherence deviations in schizophrenia patients during the resting state.
Methods: Twelve patients diagnosed with schizophrenia and twelve healthy control subjects were studied. A ten minute resting state MEG brain scan was performed with eyes open. MEG coherence analysis was carried out to determine the cortical areas that interacted strongly within each frequency bin of 2Hz from 1-50Hz. A discriminant analysis on the schizophrenia versus control coherence imaged data aimed at extracting a global pattern of network differences between groups.
Results: Statistically significant increased coherences were detected in schizophrenia patients compared to controls in the left inferior frontal gyrus (BA47), left superior temporal gyrus (BA22), left superior frontal gyrus (BA8) as well as the left lateral orbitofrontal gyrus (BA47). These areas are involved in language, memory, executive and higher cognitive functioning.
Conclusion: We conclude that resting state coherences of schizophrenia patients deviate from normal subjects in several behaviorally salient regions. Analysis with MEG coherence-imaging can provide clues to the abnormal resting state which we propose is important to understand abnormalities detected with different methods of activation.

Methods

- Twelve chronic schizophrenia outpatients meeting DSM-IV criteria for both schizophrenia and its subtype. (10 males and 2 females). Age range was 19-45 years old (mean 32±8.8 years).
  The inclusion criteria were: 1) Male or female chronic schizophrenia outpatients meeting DSM-IV criteria for both schizophrenia and its subtype; 2) Negative drug screens upon admission to the study, in addition to a corroborated history of at least one month of an illicit drug-free period prior to admission; 3) Normal neurological examinations; 4) Age between 18 and 60; 5) All medications have been constant for at least four weeks at the time of recording.
  The exclusion criteria were: 1) Patients with history of neurological disorders, including head trauma causing any period of loss of consciousness; 2) Axis II diagnoses; 3) Pregnancy; 4) Active substance abuse (positive urine toxicology or inability to verify abstinence) with the exception of tobacco dependence.
- Twelve healthy control subjects (4 males and 8 females) Age range was 19-42 years old (mean 27±6.5 years).
- 148 channels MEG : Magnetometers (4-D Neuroimaging Magnes WH2500).
- Data were sampled at 508Hz, 0.1-100Hz, then frequency filtered 1-50Hz.
- Spontaneous (Resting State) brain activity: subjects kept their eyes open for 10 minutes. During eyes open subjects fixated on a point on the ceiling of the room.
- Coherence imaging (Salmelin 2007) analysis was performed on the MR-FOCUSS-ICA (Moran et al, 2005) imaged brain activity from the resting state to identify cortical sources that interacted strongly within each of 24 frequency bands between 1-50 Hz. Freeware available at: **www.megimaging.com**

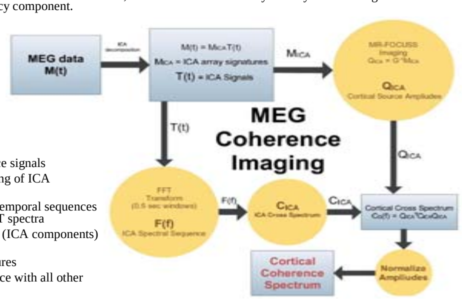
Cortical Model

Created from Volumetric MRI Data ~4,000 cortical locations gray matter

Distribution matches

Coherence Imaging

Transients and oscillations of brain electric activity are found in MEG, EEG and ICEEG recordings of spontaneous brain activity. These transient waveforms and oscillations can be quantified by applying a time-frequency decomposition technique such as the short-time Fourier transform (sFFT). After transformation to a time frequency representation, the strength of network interactions can be estimated by calculation of coherence, which is a measure of synchrony between signals from different brain regions for each FFT frequency component.



Coherence Imaging: Calculation

1. Calculate time sequence of brain activity (divide data into 7.5 sec window)
   a. ICA extraction of burst activity brain source signals
   b. MR-FOCUSS (current distribution) imaging of ICA components
2. Calculate FFT sequence (0.5 second windows) temporal sequences of sources are converted to temporal source FFT spectra
3. Calculate cross-spectral matrix between sources (ICA components) for each frequency
4. Calculate coherence between all network structures
5. For each active cortical site the average coherence with all other sources is calculated for each frequency.
6. Both the Imaginary and Real components are incorporated in the coherence imaging results.

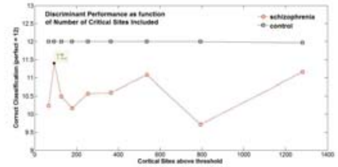
Introduction

Schizophrenia is a psychiatric disorder that affects 0.5-1% of the world's population (Kurt et al., 2011). The disorder is characterized by a wide range of symptoms including positive, negative and cognitive disturbances (Keshavan et al., 2011; Jepsen et al., 2010). To date, both the etiology and pathophysiology of schizophrenia remain elusive. The human brain's capacity for cognitive functioning is thought to depend on coordinated activity in sparsely connected, complex networks organized over many scales of space and time. Recent work has demonstrated that human brain networks modeled from neuroimaging data have economical properties that confer high efficiency of information processing at relatively low connection cost (Bassett et al., 2009). Moreover, neural networks dysfunction accounts for a wide range of problems in schizophrenia, from psychosis to cognitive deficits (Ford et al., 2007). In order to fully understand brain activity deviations during specific cognitive or behavioral tasks, deviations during the resting state (the initial state in most studies) must be fully understood (to differentiate what is resulting from activation). As of writing this report, there continues to be paucity of data regarding resting state utilizing MEG methodology. MEG methodology offers an expanded ability to detect deviations resulting from brain regions that may not as easily detectable by EEG (Barkley, 2004). In the era of brain stimulation, identification of areas of consistent hyper or hypo-activation may open the doors for novel treatments.

In the current study our a priori prediction was the detection of persistent activation of a loop in the resting-state network involving regions in frontal and cingulate areas. Secondly, we hypothesized laterality differences between patients and control subjects.

Discriminant Analysis

Discriminant analysis was used to quantify global differences in brain network function between groups. As a test for significance of these global differences, a non-parametric statistical approach showed that the whole brain connectivity pattern of schizophrenia is different from controls relative to resampled groups where differences are due to random variation across subjects.



Graph 1: Discriminant performance at different levels of thresholding (i.e., number of sites included in the analysis) quantifies the number of correct classifications for Schizophrenia and Control groups.

- Ho-Kashyap Discriminant analysis was used (Duda R.O. et al, Pattern Classification, John Wiley & Sons, Inc.).
- To test for significance of a discriminant pattern relative to no difference between groups, 5000 sets of Group1 and Group2 were created where each was composed of 6 schizophrenia patient coherence data and 6 control coherence data where the composition of the groups was determined by random assignment. Then the average coherence for each group was calculated using two versions of the total difference between group averages. The first version maintained the signed difference for all cortical sites. For the second measure of difference, the absolute value of individual cortical coherence differences were summed over the whole brain.
  Statistical p-values are based on groups of 12 subjects with 6 randomly chosen from each group. Thus, the 5000 group differences incorporate the random variability of the 24 subjects, but eliminate differences due to identification as schizophrenia or normal. P-values for the actual difference between schizophrenia and control subjects were calculated by how this difference ranked relative to the ranks of the 5000 random group difference amplitudes. So, the limit on p-value resolution was 1/5000.

Image Results

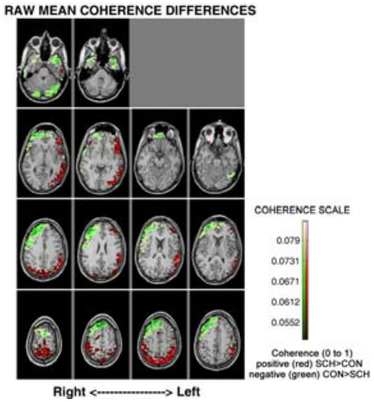


Figure 1. Raw mean coherence differences between schizophrenia and control group.

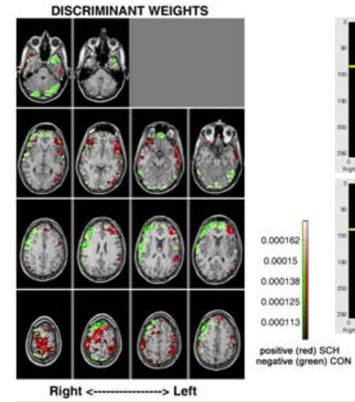


Figure 2. Discriminant analysis weights in comparison between schizophrenia and control group.

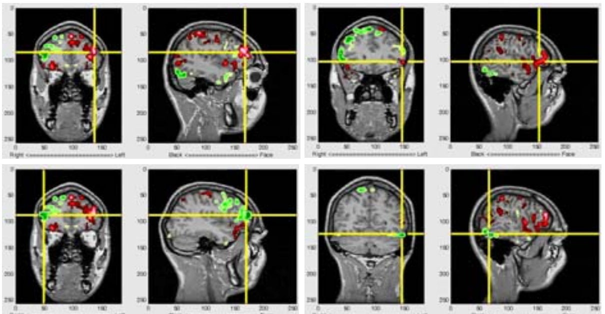


Figure 3. Areas with larger discriminant weights for schizophrenia group (top images) and control subjects (bottom images).

Conclusions

- Our preliminary MEG findings suggest possible biomarkers/indicators of an abnormal resting-state in schizophrenia patients.
- As no task performance or cooperativeness is required (other than staying still during recording) this procedure may be useful in uncooperative or significantly cognitively impaired patients.
- Furthermore, resting-state indicators recorded by MEG can be used to quantitatively assess brain activation levels pre- and post-treatments in patients with schizophrenia.
- Though there is more left-sided mean coherence of regions in the frontal lobe in patients with schizophrenia, it remains to be seen where other areas of the brain may be aroused during the experience of certain active symptoms of the disease: auditory hallucinations, visual hallucinations, etc.
- Few drawbacks limit the generalizability of the results. First, it is the small sample size. Definitive correlations with clinical symptom-clusters could not be provided. Secondly, patients were medicated with various antipsychotic agents (majority on atypical antipsychotics). The effects of medications on the MEG signal are currently not well-known. Thirdly, there was an unmatched distribution of gender in our samples of schizophrenia patients and healthy controls. Furthermore, as in coherence imaging results, the localization of imaged brain activity is strongly dependent on the frequency bands with greatest power, investigation of coherent activity at narrow preselected bands is warranted.

References and Acknowledgment

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