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Neural Connectivity Analysis by using 3-D TMS-EEG with Source Localization and Sliding Window Coherence Techniques

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ABSTRACT

Studying electroencephalography (EEG) in response to transcranial magnetic stimulation (TMS) is gaining popularity for investigating the dynamics of complex neural architecture in the brain. For example, the primary motor cortex (M1) executes voluntary movements by complex connections with other associated subnetworks. To understand these connections better, we analyzed EEG signal response to TMS at left M1 from schizophrenia patients and healthy controls and in contrast with resting state EEG recording. After removing artifacts from EEG, we conducted 2D to 3D sLORETA conversion, a well-established source localization method, for estimating signal strength of 68 source dipoles or cortical regions inside the brain. Next, we studied dynamic connectivity by computing time-evolving spatial coherence of 2278 (=68*(68-1)/2) pairs of cortical regions, with sliding window technique of 200ms window size and 20ms shift over 1sec long data. Pairs with consistent coherence (coherence>0.8 during 200+ sliding windows of patients and controls combined) were chosen for identifying stable networks. For example, we found that during the resting state, precuneus was steadily coherent with middle and superior temporal gyrus in the left hemisphere in both patient and controls. Their connectivity pattern over the sliding windows significantly differed between patients and controls (p-value<0.05). Whereas for M1, the same was true for two other coherent pairs namely, superamarginal gyrus with lateral occipital gyrus in right hemisphere and medial orbitofrontal gyrus with fusiform in left hemisphere. The TMS-EEG dynamic connectivity results can help to differentiate patient and normal subjects and also help to better understand the brain architecture and mechanisms.

Keywords: EEG, TMS, source localization, neural network connectivity

1. INTRODUCTION

Survivors of combat experience, terrorist attacks, natural disasters, serious accidents, assault or abuse, or even sudden and major emotional losses can suffer from psychobiological mental disorder. Trauma, sensory gating deficits, high stimulus response and sensitivity are very common in such mental illnesses. An individual with sensory gating deficits lacks the physiological process of filtering out unnecessary sensory information. Sensory gating deficits in mental illnesses such as schizophrenia are extensively studied, which have also produced useful biomarkers that act as the baseline[1,2]. However, therapeutic techniques for treating such ailments are still unknown. Transcranial Magnetic Stimulation (TMS) as a potential treatment plan has recently gained a lot of popularity. However, it's consequent effect to the cortical activity is still not clearly understood, which hinders its usage as an effective treatment and raises concerns for safety[3]. Efforts in this direction are better explored with electroencephalography (EEG).

EEG is a non-invasive neuroimaging technique that offers high temporal resolution unlike any other neuroimaging technique[4] thereby making it the best candidate for deriving causal relationship given that the trillions of neural synaptic connections inside our brain happen at the milliseconds scale. Analyzing EEG with source localization algorithm, a 3D inverse technique to predict source dipoles inside the brain for the given EEG data, improves spatial resolution information for further better analysis.

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Here, we studied EEG based source localized data in response to TMS subthreshold stimulus administered at the left motor cortex of 6 healthy controls and 6 schizophrenia patients to generate critical spatial and temporal conclusions across controls and patients. We compared this with that of the resting state.

2. METHODS

2.1 Experimental Procedure, EEG data gathering and preprocessing

TMS was administered at the left motor cortex of 6 healthy controls and 6 schizophrenia patients. Their EEG response was recorded from 11 cortical electrode sites as shown in figure 2 for 60 trials each 4sec apart. For resting state, EEG was recorded without the TMS where the subject was simply asked to be in a relaxed state with eyes open during the data gathering. EEG was then processed for artifact removal by applying a 1-50Hz band pass filter and a peak to peak threshold value of 100μV in a sliding window technique with a window size of 200ms with 50ms shift in MATLAB based EEGLAB and ERPLAB toolbox[5,6]. The epoch size for each trial was chosen to be 1000ms post 50ms of the TMS pulse to avoid the very noisy part of the data.

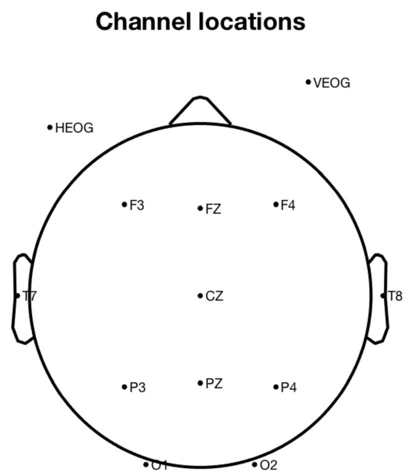


Figure 1 Layout of (approximate) location of electrode sites used for recording EEG response from 12 subjects to TMS administered at the left motor cortex.

2.2 EEG source localization and connectivity estimation

We used the sLORETA algorithm[7] implementation with the open source MNE-Python library[8,9] for performing source localization on each EEG epoch data. sLORETA, abbreviated for standardized low-resolution brain electromagnetic tomography, is a standard technique to solve the inverse problem at a spatial resolution of 5mm based on the digitized Talairach atlas provided by the Brain Imaging Centre Montreal Neurological Institute[10] to estimate source current density inside the brain for the given EEG data as shown in figure 2. We then calculated coherence for each pair of estimated source current density with a sliding window technique on each epoch as shown in figure 3. Coherence computation was based on the unambiguous brain interaction approach formulated by Nolte et al[11], which is given as:

$$C_{ij}(f) = \frac{S_{ij}(f)}{\left(S_{ii}(f)\,S_{jj}(f)\right)^{\frac{1}{2}}} \qquad (1)$$

The sliding window coherence technique enables the analysis of causal temporal dynamics from the 68 estimated sources. For transient analysis of response to TMS at the M1 cortical area, we chose window size as 200ms with 20ms shift over the 1000ms long epoch, resulting in coherence values based on equation (1) for 2,278 pairs of estimated sources for 41 windows for each subject. We performed a group-based analysis for both patients' and controls' group. Hence, we get a total of 246 time windows by taking time windows of 6 subjects together for a group as shown in figure 4. If 200 or more windows, in the two groups combined, had coherence values equal to or higher than 0.8, we identified that as a consistently coherent pair of sources and hence, it was marked that as a constituent of a stable network. For these stable pairs, 2 sample t-test was performed to check for significant differences between the two groups (patients and controls) for their causal temporal coherence dynamics.

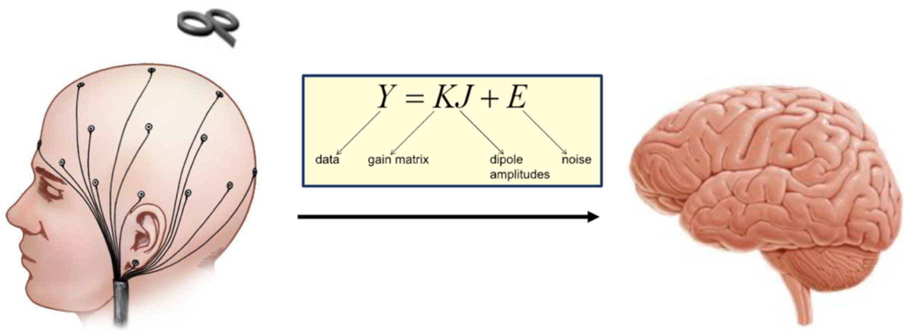


Figure 2 By using the sLORETA algorithm, a well-established technique for source localization, we studied three-dimensional signal propagation inside brains, 68 cortical regions, from EEG response to a single TMS subthreshold (80%) pulse targeted at the left motor cortex of 6 schizophrenia patients and 6 healthy controls.

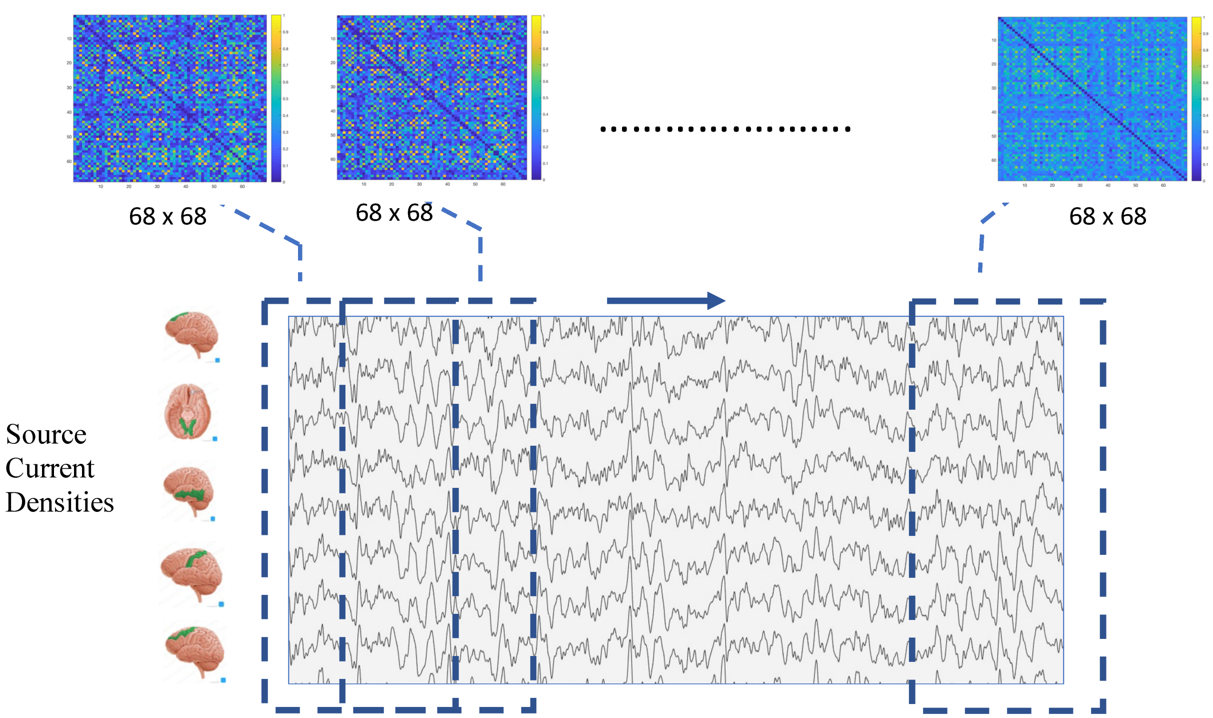
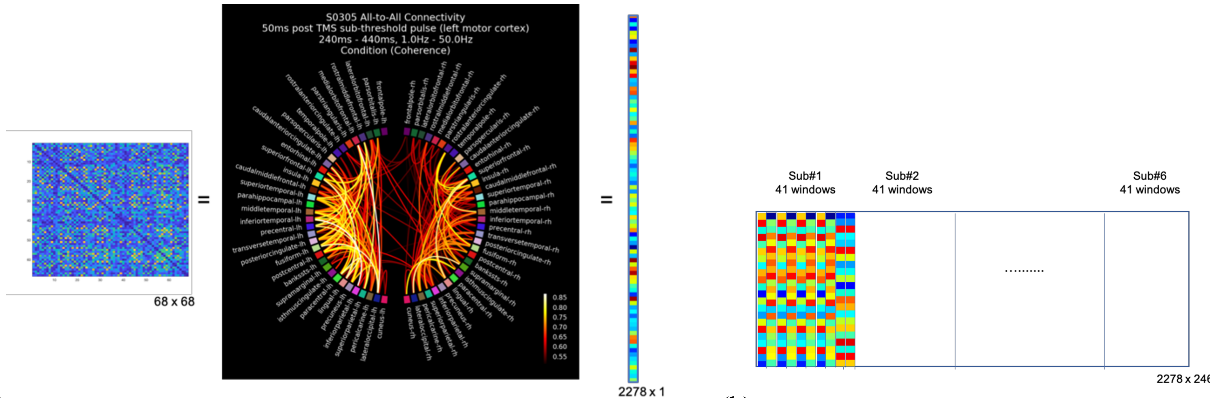


Figure 3 The dynamic connectivity was studied by computing time-evolved spatial coherence, for 2278 pairs of cortical regions' current densities, with sliding window technique of 200ms window size and 20ms shift (total 41 windows), a much higher temporal resolution than that of fMRI.



(a) (b)

Figure 4 (a) For each epoch's estimated source current density, a sliding window coherence was calculated resulting in 2278 pairs of coherence values over 41 time windows for each subject (a sample sliding window is shown here that has coherence values among 68 localized sources). This way, we get (b) 246 time windows of 2278 coherence values for each group of patients and controls.

3. RESULTS AND DISCUSSION

Table 1 summarizes the coherent pairs from resting state and table 2 summarizes the coherence pairs during the M1 stimulation. During the resting state, we see that the precuneus was steadily coherent with middle and superior temporal gyrus in the left hemisphere for both patient and controls. Their connectivity pattern over the sliding windows significantly differed between patients and controls (p-value<0.05). Whereas during TMS on M1 cortex, the same was true for two other coherent pairs namely, superamarginal gyrus with lateral occipital gyrus in right hemisphere and medial orbitofrontal gyrus with fusiform in left hemisphere. These regions are displayed in figure 5.

Table 1: Results from analysis of 5 controls 5 patients resting state

Region of interest (ROI)		**p-value from 2 sample t-test on boolean data (1 if coherence>0.8 else 0)**	**p-value from 2 sample t-test on actual coherence values**	**Number of sliding windows where coherence>0.8**		
1st element of the pair	**2nd element of the pair**			**Controls**	**Patients**	**Controls and Patients combined**
Superior Temporal Gyrus (left hemisphere)	Precuneus (left hemisphere)	0.00082174	0.014211447	151	119	270
Precuneus (left hemisphere)	Middle Temporal Gyrus (left hemisphere)	4.51E-02	0.005671146	110	130	240

Table 2: Results from analysis of 6 controls 6 patients M1 stimulation

Region of interest (ROI)		**p-value from 2 sample t-test on boolean data (1 if coherence>0.8 else 0)**	**p-value from 2 sample t-test on actual coherence values**	**Number of sliding windows where coherence>0.8**		
1st element of the pair	**2nd element of the pair**			**Controls**	**Patients**	**Controls and Patients combined**
Medial Orbitofrontal Gyrus (left hemisphere)	Fusiform Gyrus (left hemisphere)	0.007754685	0.001289767	115	86	201
Supramarginal Gyrus (right hemisphere)	Lateral Occipital Gyrus (right hemisphere)	1.43E-27	2.42E-08	178	64	242

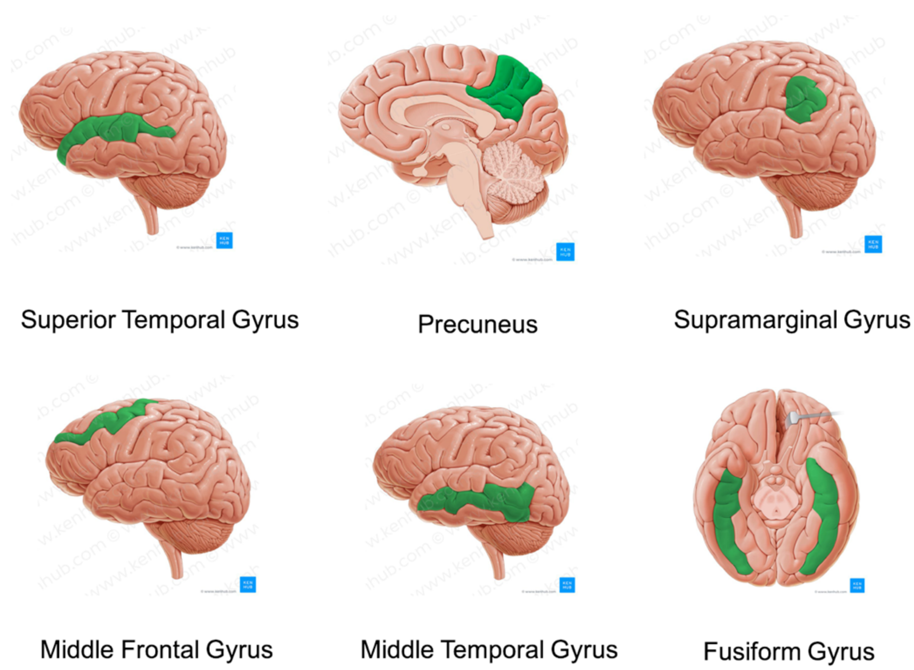


Figure 5 Cortical regions involved in stable networks as summarized in table 1 and table 2. (Medial Orbitofrontal Gyrus and Lateral Occipital Gyrus are not shown here)

4. CONCLUSIONS AND FUTURE SCOPE

We analyzed EEG based source localized data during the resting state and M1 cortex TMS stimulation state. We reported stable subnetwork of cortical regions that significantly differed in their temporal dynamics for patients and controls during TMS and resting state. These TMS-EEG dynamic connectivity results can help to differentiate patient and normal subjects and also help to better understand the brain architecture and mechanisms for the future medicinal applications with TMS. In future, we plan to use these methods for analysis with larger number of channels and subjects.

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