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Abstract:

Electroencephalography (EEG) is widely used to characterize the temporal patterns of electrical activity, primarily associated with neocortex. Traditionally, the sensitivity of EEG to cerebellar activity has been considered limited with the electrical potentials assumed to stem from cortical pyramidal cells. This study leverages recent work examining the structure, organization, and synchrony of purkinje neurons to promote local field potentials measured by EEG. In conjunction with high fidelity EEG recording and source imaging analysis we examined the feasibility of using current EEG systems to characterize cerebellar function in a series of simple motor tasks. Distributed source imaging analysis revealed consistent task-related cerebellar activity across subjects whose time course was consistent with cerebellar involvement for the control of voluntary movement. The results demonstrate the feasibility of using current EEG systems and source imaging techniques to resolve activity in the cerebellum that is distinct from task-related activity in cortex.

SECTION I. Introduction

Electroencephalography (EEG) has been used extensively to characterize the temporal patterns of neural activity in the neocortex, providing important insights into brain function. However, long held assumptions regarding EEG have suggested it is significantly less informative about neural activity in the cerebellum. The cerebellum is a fundamental structure in the brain, containing approximately eighty percent of neurons [12]. Neurophysiological, behavioral, and imaging studies support key roles in the control of movement, prediction of sensory inputs and the consequences of motor outputs, as well as basic cognitive tasks [12]. Despite this, understanding of the cerebellum's temporal dynamics, and thus function, remains limited even with modern neuroimaging techniques. This study examines the feasibility of using EEG to help address this gap in knowledge by leveraging advances in high fidelity EEG recording and source imaging analysis techniques.

As a neuroimaging tool, EEG provides a high temporal resolution measure of brain activity that is complementary to magnetoencephalography (MEG) and relatively low-cost at the expense of reduced spatial resolution [9], [10]. Because of this, almost a century after its creation, EEG is still a prominent modality in neurological research. EEG is most sensitive to synchronous activity of the inputs to a brain region, often characterized by Local Field Potentials (LFPs). The source of LFPs are thought to arise primarily from the neocortex. Moreover, the LFPs measurable by EEG are assumed to be attributed primarily to the synchronous activity within networks of pyramidal cell whose parallel spatial organization facilitates the summation of electrical currents to levels detectable at the scalp.

As with any neuroimaging technique, EEG has strengths (high temporal resolution) and limitations (e.g. lower spatial resolution). In its raw form, EEG is limited in its ability to spatially differentiate active brain areas and is typically assumed to be limited to measuring the activity of the neocortex [11]. EEG's limited spatial resolution has been addressed in part through the application of source localization techniques designed to solve the inverse problem. The presumption that EEG reflects activity in neocortex remains in spite of advances in EEG system sensitivity and signal processing techniques [3], [6], [7]. This has led to a strong cortical focus when conducting EEG source imaging studies.

Similarities in the neurobiology of neocortical pyramidal cells and neocerebellar purkinje cells, suggest that pyramidal cells may not be the only source of measurable LFPs at the scalp [11]. Purkinje and pyramidal cells both demonstrate parallel organization, orthogonal orientation to the tissue surface, and tend to respond synchronously with spatially nearby cells [2], [8]. These parallels suggest that it should be possible to use EEG to measure neural activity in the cerebellum. Despite this, EEG inverse and forward modeling techniques remain focused on cortex to the extent that cerebellum is typically not included as an anatomical structure for source imaging analysis, particularly for surface-based source imaging.

In this paper, we report EEG source imaging results from a series of simple motor flexion tasks that demonstrate task-related cerebellar activity which is distinct both spatially and temporally from source activity measured in motor cortex. We show that the patterns of task-related activity are consistent with fMRI studies of cerebellar function, demonstrating ipsilateral activity in response to motor tasks.

SECTION II. Methods

A. Subjects and Approach

Fifteen subjects participated in the study (9 male, 6 female; ages 19-28). All subjects provided written informed consent according to the Institutional Review Board at Marquette University. Subjects' EEG activity was measured using a 64-channel BrainVision Easycap with a BrainAmp MR amplifier sampling at 5kHz (BrainProducts, Munich, Germany). Prior to analysis, EEG signals were low-pass filtered at 1kHz to minimize high frequency aliasing and down-sampled to 500Hz for further preprocessing. EEG electrode impedances were kept below 25 kΩ to minimize the impact of electrical noise. Electrode locations were digitized for 11 out of 15 subjects using the Polhemus Fastrak system.

During the experiment, subjects were seated in front of a computer display that presented a static fixation point. While subjects fixated the screen, a series of auditory tones were presented in LabView to cue subjects to perform a single wrist or ankle flexion. Subjects participated in 360 trials spread equally across four task blocks. In each block subjects were randomly cued to flex either their wrist (left or right) or ankle (left or right), such that 90 trials were collected for each wrist and ankle movement. A flag was inserted into the EEG data at the time of each cue presentation to enable epoching and trial averaging of the evoked response. The LabView script interfaced directly with an NI DAQ to output a 0-5V square wave to the EEG triggering system, which inserted the flag in the raw data.

B. Preprocessing

EEG data was pre-processed using BrainAnalyzer 2 (BrainProducts, Munich, Germany). An 8th order bandpass filter was applied from 0.1 to 50Hz with a separate notch filter at 60 Hz to remove powerline frequency noise from the continuous data. Temporal ICA was then performed on the EEG time series to remove artifactual components. The process was repeated a second time to identify secondary artifactual components whose spatial distribution (and/or time series) may have been over-parsed due to the presence of components with large signal artifacts. Artifactual components were selected manually using component energy values and the spatial patterns of the activity across electrodes to identify common artifacts. EEG time series were then epoched from -400ms and +1200ms relative to movement cue onset. Bad channels were then removed and trials in which the measured potential exceeded ±100µV were labeled as bad and removed from analysis. Finally, trials were baseline corrected, averaged, and the average time course was re-referenced to a common average for source imaging analysis. Across subjects, an average of 4.7% of trials were removed across tasks and an average of three channels per subject were removed from analysis.

C. Source Imaging

Source imaging analysis was performed using Brainstorm 2018 (Tadel et al. 2011), which is available for download under the GNU general public license (http://neuroimage.usc.edu/brainstorm) [4]. The standard ICBM152 anatomy included in Brainstorm was used to construct the head model for source imaging analysis across all subjects. Since the standard ICBM152 head model did not include the cerebellum as part of the forward model, the cerebellum was extracted from the ICBM152 aseg atlas. The cerebellum model was then down-sampled to 10,000 vertices and the cortical and cerebellar surface models were merged. During distributed source imaging analysis, current dipoles were located at the vertices of the cerebellar and cortical surface models and constrained to orientations orthogonal to their respective (i.e. cortical or cerebellar), surfaces. For the cerebellar surface model, the orthogonal dipole constraint led to an increased spatial focus in source localization. Subsequent tests using unconstrained cerebellar dipoles demonstrated greater sensitivity to source activity in cerebellum at the expense of spatial focus. Using the combined cortical-cerebellar anatomy, a BEM model was generated using OPENMEEG's symmetric BEM technique [5]. Subject-specific electrode locations were then registered to the head model and used together with the BEM model to generate a leadfield matrix for each subject prior to source imaging analysis. For the subset (=4) of subjects without detailed electrode locations, the BrainVision Easy cap electrode template was mapped onto the head model ICBM152, both available in BrainStorm.

Source imaging was performed using a weighted-minimum norm estimate applied to the combined cortex and cerebellum model. Electrode noise, which was assumed to be independent, was estimated from the baseline interval of the trial timeseries, resulting in a diagonal noise covariance matrix. Since dipole orientation was constrained in the cortex and cerebellar models, inverse estimates were limited to the signed amplitude of the current dipole. Following source localization, current dipole amplitudes were normalized vertex-wise relative to baseline, and used to generate source maps with z-score values for each condition and subject. Finally, the group average z-score map was generated for each task condition by averaging the absolute z-score maps across subjects.

D. Region of Interest (ROI) Analysis

Task-relevant ROI's were defined in the motor cortex using the aseg atlas in BrainStorm. The motor cortex in each hemisphere was subdivided into two ROIs corresponding to the precentral and paracentral gyrus. In the wrist condition, the precentral gyrus was of interest due to the functional activation map of wrist activity being more central. While for the ankle condition, the functional map made the paracentral gyrus of interest. The time course of activity within each ROI was then characterized using the maximum amplitude vertex across the task interval.

SECTION III. Results

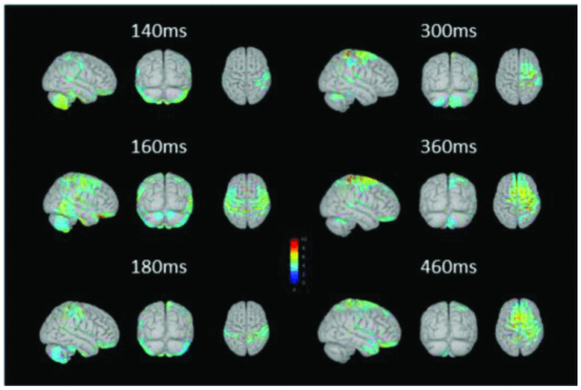

Figure 1. Group average spatiotemporal patterns of activity for the left wrist flexion condition.

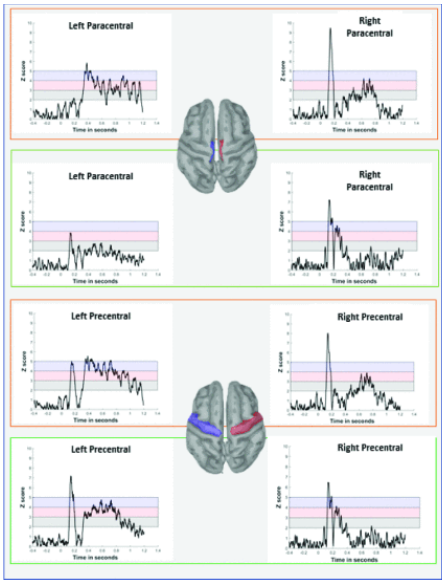

Figure 2. Time course of group average activity in each cortical ROI for right and left ankle flexion. Activity is shown for the maximum amplitude vertex within each ROI during the task epoch.

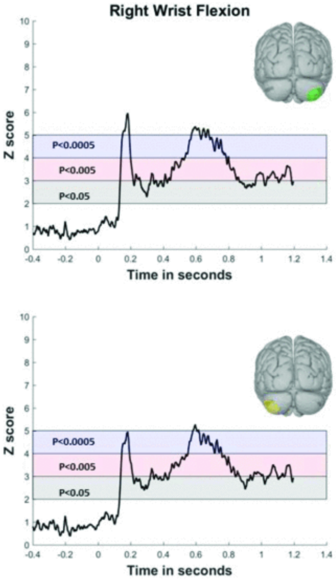

Figure 3. Time course of group average activity in the cerebellar ROIs for right wrist flexion. Activity is shown for the maximum amplitude vertex within each ROI during the task epoch.

Figure 1 shows the spatial distribution of significant activity (p<0.001) in cortex and cerebellum for six sample time points during left wrist flexion. Time points are defined relative to movement cue. Task-related cortical activity was present in the contralateral motor cortex (140 and 300ms) and bilaterally in temporal cortices in response to the auditory cue (160ms). Bilateral cerebellar lobe activity was observed early (140–180ms) on the lateral surface and followed by posterior cerebellar activity with an ipsilateral emphasis at 300ms.

Figure 2 shows the time course of cortical activity in the motor cortex ROIs for left and right ankle flexion. The expected contralateral activity was seen for the left and right ankle flexion tasks. During left ankle flexion, significant activity was observed 150–200 ms after the movement cue with greater activity in the right paracentral gyrus. During right ankle flexion, the left paracentral gyrus exhibited a lower amplitude but longer duration of significant activity than the right, while the left precentral gyrus demonstrated a larger amplitude than the right precentral gyrus. It is important to note that the proximity of left and right ankle regions on the paracentral gyrus may have led to a similar signal being present in their regions. Despite this, however, contralateral activity was still present in paracentral and postcentral gyri for both the right and left ankle conditions.

Figure 3 shows the time course of right wrist flexion for posterior Cerebellar ROIs. For the right wrist flexion condition, significant task-related ipsilateral activity ($p<0.005$) was observed at approximately 180ms in the right cerebellar ROI for the group average and 9 out of 15 of the subjects. Across subjects, the activity associated with the right cerebellar lobe was approximately 9% higher than that observed in the left cerebellar lobe for all conditions.

SECTION IV. Discussion

Using a simple motor task in conjunction with EEG source imaging, our results show task-related cerebellar source activity that is consistent temporally and spatially with a cued voluntary movement. Activity in the right posterior cerebellum was greater during right wrist flexion indicative of expected ipsilateral activity (figure 3). For most subjects, (9 out of 15) activity in the ipsilateral posterior Cerebellum was larger during the initial movement than for the contralateral posterior Cerebellum. However, for the group average activity in the right posterior Cerebellum tended to be larger across conditions.

As illustrated in Figure 2, source imaging during ankle flexion condition showed a strong contralateral focus of activity in motor cortex early during the movement period. This result is consistent with previous reports of motor activity during a simple motor task [10], and in conjunction with the observed cortical patterns of activity (i.e., Figure 1, 2) [12], suggest that the task-related cortical sources were properly localized.

Interestingly, task-relevant cerebellar activity was also identified consistently across tasks. The presence of significant ($p<0.0001$) activity ~150ms after the movement cue, is consistent with prior reports for the onset of motor-related cerebellar activity [13], [14]. The spatial pattern of activity also supports a cerebellar focus with ipsilateral activity present across movement conditions and group averages (e.g., Figure 1). The ipsilateral activity in cerebellum is consistent with fMRI studies [1], although it is important to note that the differences in temporal resolution preclude a direct mapping between time course of task-related EEG and fMRI activity.

The morphology of the time series signal in the cerebellum was also distinct from the cortical ROIs, supporting the notion that the cerebellar activity was not simply mis-localized source activity from the cortex. Finally, the experimental design was structured to minimize the likelihood for mis-localization of cortical activity on the cerebellum. By having subjects continuously fixate a sparse visual display, the experiment minimized evoked visual activity most likely to be mis-localized to the cerebellum. The use of an auditory cue provided also well characterized and cortically identifiable sensory input that was spatially distant from the cerebellum.

To our knowledge, this is the first study to investigate cerebellar source localization using a standard EEG setup during an event-related task. Recently, Todd and colleagues examined the feasibility of measuring cerebellar LFPs using a focused electrode arrangement [13]. While their study did not use source localization, it does support the feasibility of using surface-based measures of electrical activity to characterize cerebellar function. In addition, several electrophysiological studies [8], [13] have report response times for purkinje cells (~150 ms) that are consistent with the onset of cerebellar activity observed here. These results suggest that current source imaging techniques coupled with high fidelity EEG may be capable of measuring certain types (i.e. lateral and posterior) of cerebellar activity.

Future studies should examine the feasibility of using more complex sensorimotor tasks, development of inverse and forward techniques that optimize cerebellar source localization and extending the analysis to include multiple imaging modalities. Progress on these fronts, could significantly improve understanding of the human cerebellum, and its temporal interactions with neocortex, to improve treatment of cerebellar and cortical disorders.

SECTION V. Conclusion

The cerebellum has been shown to be involved both in sensori-motor function and cognitive tasks, and as such its role in healthy and affected persons is key to understanding brain function. However, a full understanding of the temporal dynamics of human cerebellum function is lacking. In this study, we demonstrated the feasibility of source localizing ERPs onto the cerebellum using modern EEG systems and source imaging techniques. With this study as a platform, EEG analyses may be expanded to improve understanding of the cerebellum and its temporal interactions with cortex to improve assessment and treatment of cerebellar disorders.

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