

Introduction

Tuberous Sclerosis (TS) is a genetic disorder that affects multiple organ systems and is associated with growth of non-malignant hamartomas throughout the body. The disease is highly associated with seizures, cognitive impairments, and behavioral or social deficits such as ASD or ADHD.

There have been various studies examining the association between TS and intellectual and behavioral outcomes for young patients using event related potentials (ERPs) obtained on EEG. This includes the Mismatch Negativity (MMN) ERP. The measurement of these potentials is a reliable, non-invasive method to compare brain activity patterns across subjects. Following from previous study data, we want to explore specific, altered patterns of electrical activity in TS patients with ASD that are distinct from those found in TS patients without ASD.

Objectives

Our objectives were to compare MMN data between TS cases with and without co-occurring ASD and Controls, as MMN may be associated with pre-attentive cognitive operations associated with ASD. Based on findings from prior studies demonstrating larger event related potential amplitudes in certain electrodes in a tuberous sclerosis with autism spectrum disorder (ASD) group, we hypothesized that the TSC+ASD group would have larger MMN amplitudes than the TSC-ASD or Controls across electrode sites, but the groups may not differ in MMN latency.

We also aimed to look dimensionally at associations with a limited range of variables in the TSC group, including ASD symptom severity, sensory symptom profile, and epilepsy. We predicted that ASD symptom severity and epilepsy severity scores will be associated with higher MMN amplitudes.

Our specific aims for this study were to:

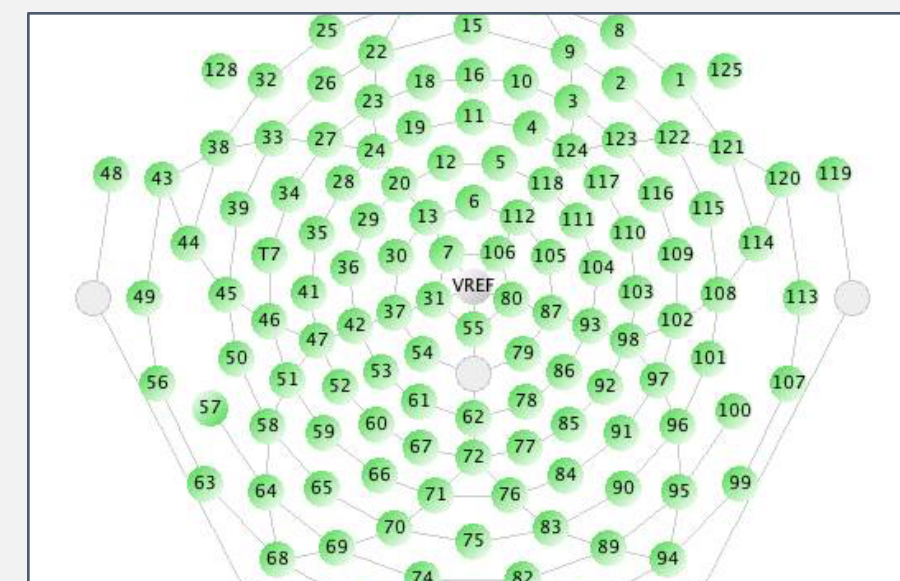
- 1) Analyze patterns of MMN event related potentials (ERPs) in a database of about 120 patients enrolled in the TS2000 study to compare amplitudes and latency between TS-ASD group and TS+ASD group
- 2) Perform regression analysis to compare epilepsy and social and sensory symptoms as related to MMN amplitudes and latencies

Methods

Subjects: Subjects came from a database of 196 TS subjects, 17 controls, 4 siblings of TS subjects. A total of 46 subjects (across all categories; 15 controls, 31 TS) with MMN data were selected for initial analysis. Participants were excluded if their ERP data fell outside of 3 standard deviations from the group mean for any category (electrode type x amplitude/latency).

Task and Stimuli: Participants completed a passive auditory task during EEG recording. Auditory stimuli consisted of standard tones (1000Hz tone for 50ms) and three deviant tones: Deviant-Frequency (1500Hz frequency for 50ms), Deviant-Duration (1000Hz frequency for 100ms), and Deviant-Frequency-Duration (1500Hz for 100ms). A total of 1400 auditory stimuli were presented. Participants watched a silent cartoon throughout task. Total task duration was 13 minutes.

Electrophysiological Recording: EEG was recorded using a 62 active electrode recording system. The reference electrode was positioned at FCz. Data were analyzed in Brain Vision Analyzer. EEG waveforms were manually filtered to exclude unclean tracings and put through a series of steps for normalization to be compatible with SPSS.



Electrode map of HydroCel used in EEG acquisition

Data Analysis: All analysis was done using SPSS. First, we performed a mixed-model ANOVA/ANCOVA with electrode site (FCz, Fz, Cz) as within-subjects factor, group (TSC+ASD, TSC-ASD, Controls) as the between-subjects factor, and either MMN amplitude or MMN latency as the DVs. The analysis was then covaried using variables of age and IQ. We then computed the average MMN amplitude and latency (across the 3 sites) and computed spearman correlations between the variables of interest in the TS+ASD and TSC-ASD groups.

Results

MMN means: The TSC+ASD group had larger MMN amplitudes than the TSC-ASD or Controls across electrode sites. The groups did not differ in MMN latency. The effects of amplitude and latency were unchanged when covarying with age and IQ.

ASD symptoms: Analysis showed that more severe sensory symptoms (as defined by SSP scores) were associated with larger MMN amplitudes and higher ASD symptoms (as defined by ADOS) were associated with increased MMN latencies.

Epilepsy symptoms: There was no significant association between current epilepsy (as defined by Seizure Severity Score) and MMN amplitudes in the TSC+ASD population vs. TSC-ASD or Controls.



Conclusions & Future Directions

The preliminary data suggest a link between auditory processing and ASD symptoms as compared to controls and those with Tuberous Sclerosis alone. Though there was no clear association with any epilepsy symptoms and auditory processing as given by MMN differences, our next steps will be to analyze other seizure symptoms, such as infantile spasms, and tuber burden in relation to MMN potentials.

With additional analysis, neurophysiological profiles of ASD and epilepsy in TSC may come to provide biomarkers that identify more general neural pathways in ASD and can direct specific therapeutic strategies.

References

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