Applying Regionalized Tessellation to Detect Diagnostic Markers of ASD in Resting EEG Data

Adham Atyabi[2,3], Takumi McAllister[1], Simone Hasselmo[1], Ariel Chang[1], Max Rolison[1], Taylor Halligan[1], Brianna Lewis[1], Talena Day[1], Kathryn McNaughton[1], Kimberly Ellison[1], Julie Wolf[1], Kayla Stinson[1], Sabrina Malak[1], Julie Trapani[1], Ela Jarzabek[1], James McPartland[1], Adam Naples[1]

[1] McPartland Lab, Yale Child Study Center, New Haven, CT
[2] Seattle Children's Innovation & Technology Lab (SCITL), Seattle Children's Research Institute
[3] Department of Pediatrics, University of Washington

Background

- Autism spectrum disorder (ASD) is a developmental disorder associated with deficits in social interaction and the presence of restricted and repetitive behaviors.
- Event-related potentials (ERPs), such as the N170 and P100, are well-known neurophysiological markers that have shown promise in differentiating individuals with ASD from typically developing (TD) individuals.
- ERP-based analysis entails the risk of constituting substantial overlap in amplitude and latency responses and the results do not take into consideration dynamic relationships between components and topography.
- Analysis of Variance (ANOVA) relies on point estimates of peak or latency of ERP components and only provides limited information regarding the precise temporal and spatial differences between groups.
- Variations of Mass Univariate Analysis (MUAs) are alternative approaches that hypothesize exchangeability of data points/conditions and rely on permutations for identifying the spatial or temporal data points that distinguish groups.
- MUA approaches are limited in that they rely on simple statistical tests (t-tests) and arbitrary choices of initial parameter settings. Furthermore, they are limited to simple point estimates of electroencephalogram (EEG) features such as peak or latency estimates.
- Our objective was to develop a new mechanism that was applicable to arbitrary EEG features, robust to family-wise error, and took into consideration dynamic relations between EEG components and topography by systematically identifying scalp regions that consistently register significant differences between groups.

Regionalized Tessellation: Why is it needed and what is the contribution?

- Regionalized Tessellation (RegTess) identifies scalp regions that show systematically different responses to the activity presented across groups.
- The RegTess methodology was developed to be insensitive to feature representation (e.g., amplitude, frequency, coherence) unlike variations of MUA that are limited to frequency and ERP analysis.
- Unlike variations of MUA that are dependent on the assumption of fixed neighboring size and minimum cluster size, RegTess does not have these limitations and considers any region that contains at least one electrode.
- While variations of MUA tend to identify localized significance within nearby electrodes, RegTess utilizes region presentation to capture significance across multiple clusters of electrodes.
- RegTess avoids permutation and is not subject to the same complications as MUA methods, such as false positive/negatives and family-wise errors.

Method

Sample

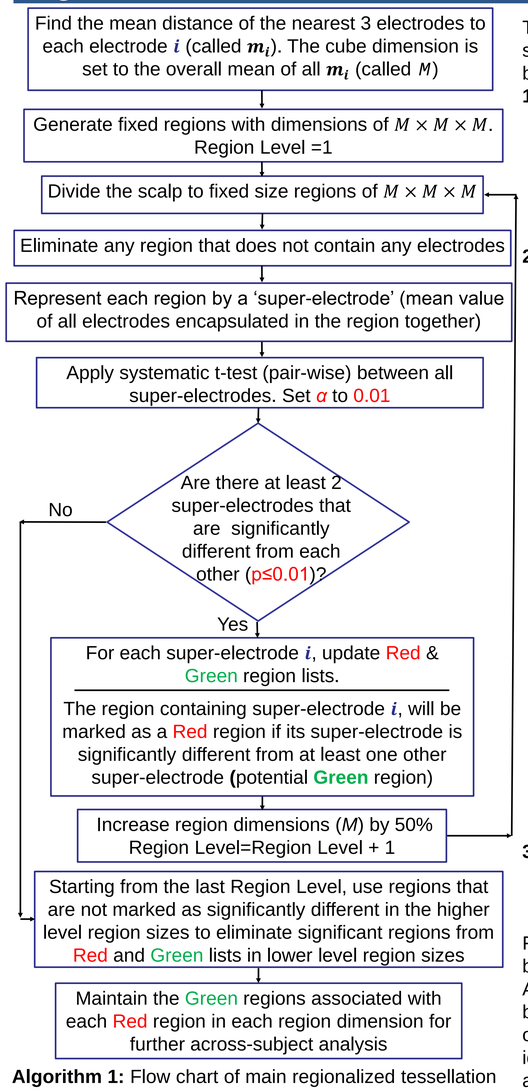
Group	Sex	Age	IQ	Max Age	Min Age	N
ASD	male	14.26	102.71	17.99	8.53	94
TD	male	13.98	104.11	17.99	8.16	40
ASD	female	13.16	102.38	16.43	9.07	36
TD	female	12.29	106.45	17.03	8.94	33

Experimental Paradigm:

- EEG was recorded continuously at 500Hz using a 128-channel HydroCel Geodesic Sensor Net.
- Participants viewed a fixation cross on a computer monitor for 1 minute and then sat with their eyes closed for 1 minute.
- The sample was composed of 130 individuals with ASD and 73 typically developing (TD) control participants.

Funding sources
The datasets, methods, and personnel in this study are supported by the following funding sources:
NIMH R01 MH100173 (McPartland), Autism Speaks Translational Postdoctoral Fellowship (Naples), Waterloo Foundation 1167-1684(McPartland), Patterson Trust 13-002909(McPartland), NIH U19 MH108206(McPartland)

Regionalized Tessellation



Algorithm 1: Flow chart of main regionalized tessellation algorithm applied separately to the amplitude correlation results of each participant in the study.

The RegTess algorithm uses the following steps to identify those regions that best reflect between group differences in EEG data:

1. **Pre-Processing**: The following preprocessing steps are applied:
   - The EEG data is converted to fixed-size non-overlapping epochs (1s here).
   - 1-100Hz bandpass filtering.
   - Prep pipeline [1].
   - Artifact detection.
2. **RegTess:**
   - **Within-Subject:** For each participant in the study, use the mechanism presented in *Algorithm 1* and generate a set of Red and their associated Green regions for each region levels considered (in our example, 5 region levels are considered).
   - **Within-Group:** Generate two region-banks containing all the regions found to be significant in TD (TD-bank) and ASD (ASD-bank) participants.
   - **Across Subjects**:
     - From each region-bank, starting from the biggest region level, maintain a subset of regions that has the highest percentage of across-participant agreement on their significance in the region-bank.
     - In each lower region level (regions with smaller dimensions), maintain a subset of only the green/red regions for which there is a majority agreement on their significance and that fit inside the maintained regions from the previous step.
3. **Aggregation of the Residual**: Considering the elected regions in each level, only maintain the subset of regions that are not common in both groups.

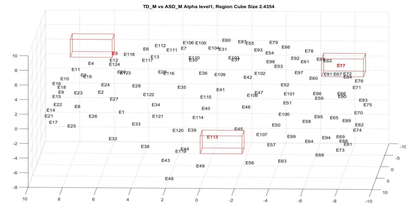
Following this mechanism, we assessed the between-group differences in resting EEG of ASD and TD participants using the alpha and beta frequency correlation as the feature type of interest. The assessment was conducted to identify regionalized differences between ASD and TD, and also male and female participants.

Preliminary Results with Alpha Amplitude Correlation

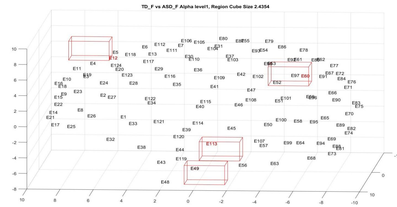
1. **Gender impact:**
   - TD: No gender-specific regionalized differences were observed in TD participants.
   - ASD: Regions containing the following electrode clusters were found to be significant but inconsistent across males and females in ASD group. [E71], [E74], [E98,E102], [E113], [E5].
2. **Diagnosis impact:**
   - TD vs ASD: Regions containing following electrode clusters were found to be significant but inconsistent across males and females in ASD group. [E23], [E49], [E113], [E71], [E67,E62,E72].

Preliminary Results with Alpha Amplitude Correlation

3. Diagnosis X Gender impact:



a) Inconsistent significant regions across male ASD and TD individuals in alpha amplitude correlation.

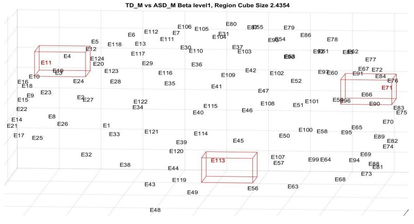


b) Inconsistent significant regions across female ASD and TD individuals in alpha amplitude correlation.

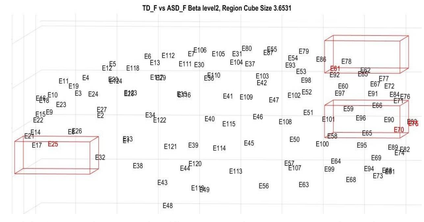
Figure 1: Inconsistent significant regions identified in (gender x diagnosis) analysis by RegTess in Alpha amplitude correlation.

Preliminary Results with Beta Amplitude Correlation

1. **Gender :**
   - TD: The following electrode clusters ([E75,E70], [E100,E108], [E21,E17], [E25]) were marked as inconsistent but significant in second level of the regions size. No gender-specific regionalized differences were observed in TD participants in smallest region size.
   - ASD: The following regions [E113],[E106] and [E11] were found to be significant but inconsistent across males and females in ASD group.
2. **Diagnosis :**
   - TD vs ASD: Regions of [E113], [E71], [E11] were found to be significant but inconsistent across males and females in ASD group.
3. **Diagnosis X Gender :**



a) Inconsistent significant regions across male ASD and TD individuals in beta amplitude correlation.



b) Inconsistent significant regions across female ASD and TD individuals in beta amplitude correlation.

Figure 2: Inconsistent significant regions identified in (gender x diagnosis) analysis by RegTess in beta amplitude correlation.

Limitations & Conclusions

- RegTess methodology relies on volume conduction of the EEG signal that results in correlated activity from different brain regions. An advantage of this methodology is its ability to identify clusters (n=1 or more) of electrodes that best distinguish groups across experimental conditions or diagnoses. This allows further in-depth analysis of across- and within-subject differences.
- Utilizing $p \leq 0.01$ as the threshold of significant validity (see algorithm 1) makes the methodology fairly conservative and robust to false positives.
- The current approach is only evaluated on resting EEG data. Further investigation is needed to fine tune the mechanism for between group analysis (e.g., ASD vs TD) and between experimental conditions in task based paradigms.
- Further analysis is required to evaluate if this approach can be used to pinpoint electrode clusters with significant across-group ERP differences over and across paradigms.

References

[1] Bigdely-Shamlo N, Mullen T, Kothe C, Su K-M and Robbins KA (2015), The PREP pipeline: standardized preprocessing for large-scale EEG analysis, Front. Neuroinform. 9:16. doi: 10.3389/fninf.2015.00016