Multi-Modal Brain Visualizations

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I. Introduction

If brain imaging techniques allow scientists to see the activities inside brains as a pair of "eyes", then data analysis is the "visual cortex" that distinguishes and values meaningful information. However, neuroscientists and psychiatrists are not necessarily data scientists, who have professional knowledge of how to create visualizations of large datasets. Data scientists, on the other hand, might not have enough domain knowledge to help them determine which visualizations would be most suitable to display clinically meaningful results. Our team would like to bridge brain scientists and data analysis by creating a web application that creates high-quality, meaningful visualizations of neuroimaging datasets including EEG and fMRI.

II. Problems to answer

A. Biomarkers Explorations

Biomarkers are a broad subcategory of medical signs, or objective indications of medical state observed from the patients that could help in identification and assay of effects of disorder risk variants as an alternative strategy. Non-invasive biomarker research in psychiatry has focused largely on neuroimaging as a tool for identifying neural functions that are meaningfully associated with psychopathology. Among the commonly used neuroimaging techniques, EEG is the most non-invasive and portable method. The cost of EEG data collection is relatively low, which means it is accessible to a large number of studies. Therefore, EEG has attracted increased interest for development of biomarkers in psychiatric diagnosis and phenotype definition. Electroencephalography (EEG) derived biomarkers haven been shown to be related to several disorders, such as depression, schizophrenia and attention deficit hyperactivity disorder (ADHD).

There are two commonly used methods for modeling EEG data that have been proven useful in identifying functional brain activity measuring differences associated with psychiatric disorders [1]. The first one is to average data across many segments that are time-locked to events of interest, that is, given a task stimulus, to produce an event-related potential (ERP) for each scalp channel. Then the electrode channel with maximum ERP expression is focused and ERP features will be analyzed and reported concerning their latency and amplitude. The other method is spectrum analysis, which could identify the mean or relative power measures for one or more EEG frequency bands of interest across a time period of interest, checking whether or not the activity is time-locked to identified experimental events.

P300, or P3, is a positively inflected event related potential (ERP) peak that occur around 300 milliseconds after a task target stimulus in the process of decision making. Reduced amplitude of P3 has been found to be associated with a number of psychiatric and behavioral disorders such as alcohol abuse and schizophrenia. Several studies have begun to validate the use of P3 as a predictive biomarker: the utility of P3 was tested with The Consortium on the Genetics of Schizophrenia (COGS-2) study across multiple sites with EEG [2]. An overall patient deficit was observed with effect size 0.62 and a significant patient deficit was observed independently for each site. In an investigation of association between P3 event-related brain potential amplitude and adolescent problem behaviors, 17 year-old twins reported whether and when they had initiated tobacco, alcohol, illicit drug use, had police contact, or had sexual intercourse [3]. Each of these behaviors was associated with reduced P3 amplitude, further validating the consistency of P3.

P50 is another ERP component that has been shown to be readily associated with schizophrenia. It also shows excellent test-retest reliability, although its use in literature as a predicative biomarker is not as common as P3. Other studies in ADHD groups also found an increased parietal P2 amplitude, a reduced frontal N2 amplitude, and a more anterior P3 compared to controls.

B. Functional Connectivity

Neuroimaging techniques could allow us to see through the skull and know what areas of brain are activiated during some specific tasks. However, they could not provide feedback of the inner processing of information across the areas as a whole.

Autism is one of the disorders that require such an "inner look". In a 2007 study by Just et.al, a group of high-functioning autistic participants and the controls showed the same cortical area activation to similar degree in fMRI. Researchers then looked at the degree of synchronization by computing the functional connectivity, or the correlation of the time series of the activation. Regions of Interests (ROIs) were paired and average time course of all the activated voxels were computed for each pair. Then correlation between the average time course was calculated as a measure of connectivity. An exploratory factor analysis was also performed for each group of ROIs so that each factor could relate to a larger network of brain regions that involve high-level functions and factor loading represent the degree to which each of the ROIs correlates with each of the factors.

In the results of the study, functional underconnectivity, especially between the frontal and parietal areas of activation,

was observed for the autistic than the control participants. This finding suggests that the neural basis of altered cognition in autism entails a lower degree of integration of information across certain cortical areas resulting from reduced intracortical connectivity [4]. Researchers further point out that the results add support to a new theory of cortical underconnectivity in autism, which postulates a deficit in integration of information at the neural and cognitive levels.

C. p-factor

In recent years, high rates of co-morbidity and overlapping therapeutic mechanisms have encouraged psychopathology research towards transdiagnostic dimensional features of clustered symptoms [5]. Studies have identified a general liability factor for psychopathology, which usually referred as the 'p factor' that underlies shared risk for a wide range of mental disorders. Researchers further investigated neural correlates that could substantiate the importance of this general liability factor, evaluating its role in characterizing the shared origins of mental disorders.

In the study by Romer et.al, p-factor was calculated through several steps [6]. Several scores for internalizing, externalizing, and thought disorder symptoms were created from corresponding self-report and diagnostic interview measures. Three different models were compared and bi-factor model was chosen at last. Then a confirmatory factor analysis was performed using the weighted least squares means and variance adjusted (WLSMV) algorithm. The WLSMV estimator is appropriate for categorical and nonmultivariate normal data and provides consistent estimates when data are missing at random with respect to covariates. p-factor was extracted through standard regression method for structural neuroimaging analyses.

Several neural correlates were found to be correlated with p-factor. p-factor is shown to be negatively correlated with white matter integrity within bilateral pons. Higher p-factor scores also map to significantly less volume of gray matter within the right and left lingual gyrus, right intracalcarine cortex of the occipital lobe and left posterior cerebellum. In a research by Elliott et.al in 2017, researchers conducted a data-driven analysis of connectome wide intrinsic functional connectivity and found higher p-factor scores maps onto hyper-connectivity between visual association cortex and both frontoparietal and default mode networks [5].

To investigate whole-brain connectivity, researchers applied connectome-wide association studies (CWAS) using resting-state fMRI. In the first step, a seed time series was extracted using Time Series Extraction. Then voxel-wise correlation was computed with Seed Timeseries and normalized to contain Z-scores via Fisher R to Z transform. A seed-based connectivity map was thus produced. Average distance between each pair of participant's functional connectivity map was then calculated and Multivariate Distance Matrix Regression (MDMR) was performed. To perform MDMR, researchers would compute Gower's centered matrix, calculate MDMR statistics for the voxel and determine significance of MDMR statistics with permutation tests.

III. Significance to us

A. Biomarker Explorations

Biomarkers could significantly benefit the identification and treatments of disorders if their validity are ensured. ERP components might be useful as biomarkers in various aspects of psychiatric treatment research. First, ERPs may serve as endophenotype markers that are closer to the underlying biology of the disease than are clinical symptoms, and they are relatively convenient to use in large-N genetic studies. Past and ongoing functional genomic projects have shown the feasibility of ERP components in multisite, large-N studies [7].

Second, ERP components could be used to help to identify potential treatment targets in preclinical research. If these biomarkers are present throughout the developments of disorders and even before the onset, they could be utilized to detect vulnerability for the disorder in potential targets. Furthermore, EEG is well suited for young children under brain developments since it is wearable, portable and non-invasive, suggesting biomarker explorations in ERP components is a good approach for detecting disorder tendency as early as in childhood.

Third, ERPs might be useful in defining subgroups within a disorder. With a list of potential ERP biomarkers taken from literature, researchers would be able to look at subgroups of patients and investigate how specific treatment would normalize the ERP impairment they show.

In conclusion, ERP components may be useful for identifying biomarkers, defining treatment targets, and for identifying individuals who are good candidates for early interventions or specific treatments. Therefore, we decide to include several exploratory visualizations for EEG, including one-to-one and aggregated plots so that brain scientists could explore EEG data and search for possible ERP biomarkers.

B. Functional Connectivity

For complicated disorders such as Autism, simply looking at activated areas in brain shown by fMRI someties does not give much information. It is not very intuitive to understand how well the communications inside brain work by looking at areas activated directly.

A measurement of connectivity, or exploration of information integrity could provide researchers with ideas of the degree that information is integrated inside brain rather than whether it is received or not. Thus, we think visualizations of the connectivity information inside brain activities would further benefit brain scientists in their data analysis processes.

In our web application, we will make a 3D plot of brain region centers colorized by numeric measure of "connectivity". In such way, brain scientists could not only obtain information of connectivity in specific regions of interest, but also visualize the whole-brain functional connectivity.

C. p-factor

P-factor provides a framework for explaining the high rates of comorbidity as well as the shared genetic variance among

categorical mental disorders. It is an original idea that is still under developments. As the new article suggests there exists a correlation between connectome wide functional connectivity and p-factor score, we would like to explore this topic more in our web application. Due to the limitation of our data, we are unable to obtain self-reports and diagnostic interviews, thus could not replicate the method researchers have been using in p-factor score calculating. However, we are curious that whether the connectome wide functional connectivity signature would still exist when we use phenotypic data such as gender and age instead of p-factor scores.

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