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FAST functional connectivity implicates P300 in working memory deficits in Alzheimer's disease. Network Neuroscience

FAST functional connectivity implicates P300 connectivity in working memory deficits in Alzheimer's disease

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***Abstract*—Measuring transient functional connectivity is an important challenge in Electroencephalogram (EEG) research. Here, the rich potential for insightful, discriminative information of brain activity offered by high temporal resolution is confounded by the inherent noise of the medium and the spurious nature of correlations computed over short temporal windows. We propose a novel methodology to overcome these problems called Filter Average Short-Term (FAST) functional connectivity. First, long-term, stable, functional connectivity is averaged across an entire study cohort for a given pair of Visual Short Term Memory (VSTM) tasks. The resulting average connectivity matrix, containing information on the strongest general connections for the tasks, is used as a filter to analyse the transient high-temporal resolution functional connectivity of individual subjects. In simulations, we show that this method accurately discriminates differences in noisy Event-Related Potentials (ERPs) between two conditions where standard connectivity and other comparable methods fail. We then apply this to analyse activity related to visual short-term memory binding deficits in two cohorts of familial and sporadic Alzheimer's disease. Reproducible significant differences were found in the binding task with no significant difference in the shape task in the P300 ERP range. This allows new sensitive measurements of transient functional connectivity, which can be implemented to obtain results of clinical significance.**

I. Introduction

Network Science approaches to the analysis of complex networks provide useful tools for the analysis of connectivity between agents [1], [2] . The brain is an example of a complex network where pair-wise dependencies between brain regions are of value in the detection of cognitive phenomena. It is found that it is neither spatial nor temporal localization of brain activity that underpins cognitive phenomena and the corresponding brain function but in fact, how the different areas of the brain are dynamically interconnected over time [3], [4]. This has led to a boom in studies of functional connectivity of brain activity across viable formats– mainly the blood oxygenation level-dependent signal in MRI and electromagnetic recordings from EEG and MEG. Here, typically, signals from parcellated regions (in fMRI) or sensors (in EEG/MEG) are subject to pairwise measures of connectivity, such as correlation coefficients, coherence measures, or phase-based measures.

The electroencephalogram (EEG) contains important discriminating information relating to sequential brain processes in response to various cognitive tasks. Providing a very high temporal resolution, scalp EEG allows for the direct recording of electromagnetic activity of the brain in a non-invasive, relatively cheap way [5]. Scalp EEG presents several notable limitations however, with the most prominent being the substantial noise levels inherent in the recorded signals. This noise poses a significant challenge, especially when attempting to investigate the functional connectivity associated with transient cognitive processes occurring within brief time-frames, typically spanning mere tens of milliseconds. A pivotal issue within the realm of functional connectivity of EEG signals pertains to the extraction of dependable connectivity estimates within these remarkably short time intervals [6]. This problem underscores the necessity for novel methodologies to overcome noise-related hurdles and facilitate the precise examination of cognitive processes unfolding at rapid temporal scales [1]. Measuring dynamic functional brain connectivity in short time windows is gaining increasing recognition in AD research due to its potential to provide information for the early detection of the devastating disease [7], [8]. An important reason for this is the growing recognition that intricate changes in brain connectivity can occur before the onset of clinical symptoms; this makes it a promising avenue for early biomarker development and a better understanding of disease progression. AD is not a static condition but involves dynamic changes in brain function, short-time based analysis with non-invasive brain imaging techniques can provide important breakthroughs in AD early detection, especially in low-income countries [9].

Despite the growing popularity of these studies, there has been limited methodological work on the analysis of EEG dynamic functional connectivity (DFC). Previous work typically focuses on the sliding window method [10], [11], [12], while this is fairly effective, the temporal resolution and susceptibility to noise is largely determined by the window size [27]. It has become a priority to simultaneously improve the temporal resolution of DFC while being robust to spurious connections and noise. Methods such as the Short-Term Fourier Transform [11] and Wavelet Analysis [13] have been frequently applied in this domain, but once again, the dependency on window size causes bottlenecks in regard to temporal resolution and

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noise robustness.

Graph Signal Processing (GSP) approaches have been employed frequently in the past to perform spectral analysis of signals in the graph domain, as opposed to the temporal domain [14]. This is achieved by computing the eigenvalue decomposition of a relevant Graph-Shift operator such as the Graph Laplacian or Adjacency matrix followed by the Graph Fourier Transform. However, the frequencies that emerge through the graph eigenvectors are still determined completely by the graph topology and do not involve the signal [1].

Here, we propose a new method for extracting reliable estimates of short-term functional connectivity. This is based on Graph Variate Signal Analysis [1], a more general framework for graph signals. Specifically, it describes how to leverage graphs of long-term reliable connectivity information to filter instantaneous bivariate node functions of multivariate signals. In essence, this emphasizes important connections and minimizes spurious ones (a well-known issue in EEG signals). This gives us a readily interpretable method to analyse the transient changes in brain activity at a high temporal resolution using pairwise connectivity measures (i.e. correlation) between EEG electrodes. Graph-variate dynamic connectivity [1] is when the long-term connectivity estimate is computed from the signal itself over the given epoch of interest so that the graph signal is directly related to the underlying graph and measurements and, therefore, solely relates to one connectivity function. Here, we develop and employ a novel methodology based on GVD connectivity which we call Filter Average Short-Term (FAST) connectivity. Essentially, FAST connectivity uses the average long-term connectivity matrix over the whole study cohort as a filter of transient functional connectivity at the individual level. Essentially, we are deriving the most consistent connections across all participants and then asking if the temporal activity associated with those connections shows differences between, for example, patients and control. As we shall see, the high temporal resolution of brain activity provided by the Electroencephalogram(EEG) [5] can now be exploited to detect more sensitive and specific cognitive changes in very short time frames.

We demonstrate the power of our novel FAST Connectivity methodology in simulations for picking out the true activity of ERPs in the presence of different levels of noise and different numbers of trials. We then apply this to the dataset containing EEG signals from the participants in the Visual Short Term Memory (VSTM) tasks [15]. Following this we perform rigorous statistical testing on temporal windows resulting from the multi-layer graph-variate tensor. This uncovers a potential biomarker for the early detection of AD as well as a potential indicator of disease progression from the EEG signals. This is a first in the formal application of GVD connectivity [1] to EEG signals.

II. Methods

A. Background

The novel method proposed is a form of graph-variate signal analysis [1]. Graph-variate signal analysis is defined formally as:

$$(\mathbf{W} \circ \underline{\mathbf{J}}_{(t)})_{ij} = \begin{cases} w_{ij} F_V(x_i(t), x_j(t)), & \text{if } i \neq j \\ 0, & \text{if } i = j \end{cases} \quad (1)$$

Where the formula defines the bi-variate analysis of the multivariate signal $\mathbf{X}$ filtered by the corresponding static matrix $\mathbf{W}$ of the graph-variate signal. $\underline{\mathbf{J}}_{(t)}$ denotes the *t*'th *n x n* matrix of $\underline{\mathbf{J}}$ and $\circ$ is the Hadamard product. Each timestep of $\underline{\mathbf{J}}$ is defined by a $n \times n$ matrix computed using the pairwise bi-variate connectivity values between signal pairs. The form of dynamic Connectivity is determined by the node function F_V. In our analysis, we used the squared difference inspired by the reformulation of the graph Dirichlet Energy [2] and also the instantaneous Pearson Correlation values as readily interpretable forms of connectivity.

Graph-Variate Dynamic (GVD) connectivity is defined as a graph variate signal analysis in which $\mathbf{W} = \mathbf{C}$ is a static adjacency matrix constructed from the long-term stable dependencies of the multi-variate signal itself. Defining our tensor for analysis from [1] as:

$$\theta(\mathbf{x}_i, \mathbf{x}_j, t) = \begin{cases} c_{ij} F_v(x_i(t), x_j(t)), & \text{if } i \neq j \\ 0, & \text{if } i = j \end{cases} \quad (2)$$

The multi-layer network θ is constructed using different relevant combinations of node-functions and long-term stable connectivity pairs.

Each c_{ij} used to construct $\mathbf{C}$ is constructed using relevant connectivity measures that give a reliable estimate for long-term term connectivity. A standard approach is the Pearson correlation coefficient computed over the whole epoch of interest:

$$c_{ij} = \frac{\sum_{t \epsilon T}(x_i(t) - \bar{x_i})(x_j - \bar{x_j}))}{\sqrt{\sum_{t \epsilon T}(x_i(t) - \bar{x_i})^2}\sqrt{\sum_t (x_j(t) - \bar{x_j})^2}} \quad (3)$$

[1]

combining this with the squared difference or instantaneous correlation as the node function, GVD connectivity is defined as:

$$\theta(\mathbf{x}_i, \mathbf{x}_j, t) = c_{ij}(\tilde{x}_i(t) - \tilde{x}_j(t))^2, \quad (4)$$

using the squared difference node function, and

$$\theta(\mathbf{x}_i, \mathbf{x}_j, t) = \rho_t(i,j) = c_{ij} \left|(x_i(t) - \bar{\mathbf{x}_i})(x_j(t) - \bar{\mathbf{x}_j})\right|, \quad (5)$$

using the Instantaneous correlation node function.

This can be considered as a representation of the amplitude and, thus, an analysis in this domain.

While we can average over a subset of nodes for a modular comparison between regions of the brain, we are more focused on a Global analysis in this paper.

B. FAST Connectivity

We now present FAST Connectivity, a novel form of Graph Variate Signal Analysis. We propose a singular filter for all participants in time-locked cognitive task-based experiments. The filter takes the long-term connectivity estimates of all

participants in the experiments and averages over them to create a single FAST filter for all participants that automatically emphasizes important connections and suppresses spurious ones in the general time-locked cognitive task of interest (in this case the VSTM binding and shape tasks). We define the FAST filter as:

Definition 1 FAST Filter

Where C is the matrix of the absolute values of the individual long-term correlation estimates, with c_{ij} representing Each entry in the matrix. For $P = 1, 2 \dots N$, where P is each participant and N is the total number of participants. We define our FAST filter as:

$$c_{ij}^{FAST} = \frac{\sum_{P=1}^{N} c_{ij}^{P}}{N} \tag{6}$$

$$c_{ij} = \left| \frac{\sum_{t \epsilon T}(x_i(t) - \bar{x_i})(x_j - \bar{x_j}))}{\sqrt{\sum_{t \epsilon T}(x_i(t) - \bar{x_i})^2}\sqrt{\sum_t (x_j(t) - \bar{x_j})^2}} \right| \tag{7}$$

[1]

We have defined our long-term connectivity estimate as the modulus of the Pearson Correlation Coefficient, this captures the long-term stable magnitude of the correlation of all participants in the task. Following Definition 1 we define FAST Connectivity as:

Definition 2. FAST Connectivity

For each $P = 1 \dots N$ where N is the total number of participants the same FAST filter is applied to each participant. The squared difference is our node function of choice.

$$\theta^{\text{FAST}}(\mathbf{x}_i^P, \mathbf{x}_j^P, t) = \begin{cases} c_{ij}^{\text{FAST}}(\tilde{x}_i^P(t) - \tilde{x}_j^P(t))^2, & \text{if } i \neq j \\ 0, & \text{if } i = j \end{cases} \tag{8}$$

FAST connectivity proposes the same filter for all participants P. This filter is constructed using the magnitude of the stable long-term correlation averaged over all participants. Essentially FAST connectivity can be defined as a Graph-Variate Signal Analysis where the long-term stable matrix is the FAST Filter and the node function is the squared difference inspired by the Dirichlet Energy.

The squared difference between signal pair values can be considered as a localized measure of the variation between signal pair values. This captures the local variation of the signal. A higher value would indicate higher variation in the signal pair region, whereas if it was small, the signal pair values are fairly constant or change smoothly in the localized region. It is important to stress that due to the nature of the squared difference node function, it emphasises anti-correlative information as higher squared difference values (that usually indicate a strong anti-correlative interaction between signal pairs) in the instantaneous connectivity profiles contribute most to the value of the mean network metrics.

On the other hand, Filtering the instantaneous correlation values with the long-term correlation coefficient of all participants gives more weight to regions where the local variation aligns with the long-term correlation patterns across participants allowing for a selective emphasis on specific features that are both locally and globally consistent. Overall, The FAST connectivity analysis is sensitive to both fine-scale variations within individual EEG signals and broader patterns shared across participants. By combining a global measure with local information, the method is effective in identifying regions that not only vary locally but also exhibit synchronized variations across participants. This should reflect meaningful functional connectivity patterns while reducing noise and spurious connectivity.

Using the absolute value of the long-term correlation coefficient for the global filter avoids cancelling out information from important connections in network averages.

This approach can enhance the detection of relevant ERPs, especially in cases where the direction of changes may vary or fluctuate between negative and positive values, providing a robust and direction-agnostic measure for identifying meaningful features in small temporal windows.

Overall, it is useful to think of the FAST filter as a 'rating' mechanism, essentially telling us which nodes are of particular interest when analyzing individual dynamic functional connectivity. This, combined with the squared difference node function, allows us to determine areas of high variation between 'important' graph signal pairs.

As mentioned before, similar to the Modular Dirichlet Energy (MDE) [2] a prototype of GVD Connectivity, FAST connectivity analyzes the temporal brain networks from a unique angle compared to other approaches such as time series analysis of network metrics. Essentially, one stable network of long-term connectivity is computed over the whole epoch, which is used as a support for localized analysis of very small temporal windows, allowing us to maximize the high temporal resolution of EEG signals. The activity is, in fact, encoded in the graph signal itself rather than the time-varying edge weights. This allows for analysis of smaller temporal windows of activity and also analysis of the overall long-term activity.

However, one clear limitation of this approach is that we lose out on potentially important short-term connectivity between otherwise unimportant long-term connections. We do not assume that such information is not important, but rather the problem of spurious correlations over short-temporal windows far overshadows it. The success of the method demonstrated in simulations and real data backs this argument.

C. Network analysis of FAST connectivity

FAST connectivity can be computed over arbitrarily selected windows resulting in a connectivity matrix for each window. We can then straightforwardly compute network analysis on these connectivity matrices. Here we use the Mean Edge Weights as well as an average Local Weighted Clustering Coefficient of FAST functional connectivity. The mean edge weight is computed as:

$$\bar{W}(t) = \frac{1}{n^2} \sum_{i=1}^{n} \sum_{j=1}^{n} \Delta_{ij} \tag{9}$$

We computed the average local Weighted Clustering coefficient for each temporal window as:

$$C_{avg}(t) = \frac{1}{n}\sum_{i=1}^{n}\sum_{j,k=1}^{n}\Delta_{ijt}\Delta_{ikt}\Delta_{jkt} = \frac{1}{n}\sum_{i=1}^{n}(\underline{\boldsymbol{\Delta}}_{(t)}^{3})_{ii} \quad (10)$$

The clustering coefficient quantifies the number of connected triangles in a network and, thus, the tendency of nodes to cluster together. This weighted version multiplies the triangle weights together, with larger values where all triangle weights are large. The average value for each temporal window emphasises the strongly clustered components in the signal. The computation is fairly straightforward with the sum of the main diagonal of the cube of the tensor divided by the number of nodes (EEG electrodes). We can make two interesting observations here, taking into account the Law of Large numbers stating that as the number of independent samples increases the empirical mean converges to the true mean we can conclude that increasing the number of electrodes and thus nodes (and thus independent samples) will give us a more stable and reliable estimate of the mean for a given time-step allowing for a greater temporal resolution, this has been implicated in previous studies, where there is strong evidence showing that as a result of reducing electrode density networks tended to get skewed [16], this effect was most prominent below 64 electrodes. Also, the Central Limit Theorem tells us that the estimate will converge to a normal distribution as the number of independent samples increases, suggesting that increasing the number of electrodes would allow the network metric estimates to follow a more Gaussian distribution, providing better estimates of the mean to allow for more robust statistical testing.

D. Simulations

We utilized open-source MATLAB functions provided by Yeung et al.[17], [18] to generate the simulated EEG data. The simulated data consists of two key components: noise and signal. The noise component is generated to mimic the power spectrum of a typical human EEG recording. The signal component is parameterized to describe the position of the centre of the peak, its frequency, and its amplitude. These parameters enable us to create sample ERPs, which serve as the basis for testing the effectiveness of our method. The EEG simulation functions provide a setup with 31 electrodes, each sampled at a frequency of 200Hz, with an epoch duration of 0.8 seconds. To generate independent samples, we averaged the random signals over varying numbers of trials, resulting in single 31x200-dimensional samples that closely resemble real EEG data.

For our experimental setup, we aimed to replicate conditions akin to typical comparisons between participants in time-locked Visual Short-Term Memory (VSTM) tasks. We created 20 independent samples consisting solely of EEG noise, aligning with the EEG power spectrum of a typical human. In parallel, we generated 20 independent samples with specific ERPs, including the N100 and P300 components. The N100 component was parameterized with an amplitude of -5 (typically negative) and a frequency of 5 Hz, with a centre position at 25 frames (around 100ms) considering the 0.8-second epoch. The P300 component was parameterized with an amplitude of 5 (positive and larger than N100) and a frequency of 5 Hz, with a centre position at 75 frames (around 300ms) within the 0.8-second epoch. To introduce realistic variability, the functions incorporate temporal jitter at the onset of the ERPs, mirroring the kind of activity observed in actual EEG ERP data. We then added random Gaussian white noise to the samples containing the simulated ERPs to test the robustness of our FAST Filtering method in the presence of variable levels of external noise. This approach allows us to rigorously test the performance of our method in distinguishing between the presence and absence of these specific ERP components in simulated EEG signals.

E. Visual short-term memory data

We use the data from Pietto et al. [9] with 10 patients having Alzheimer's due to a familial gene, which is a younger age group with Mild Cognitive Impairment (MCI) compared to 10 age and education-matched Control patients. This is a 64-electrode setup with a sampling frequency of 500Hz over a one-second epoch of binding or shape tasks. We have a second data set of Sporadic AD patients with 13 Patients with MCI due to AD due to no specific genetic cause and 17 age and education-matched controls. This is a 128-electrode setup with a sampling frequency of 255Hz with the same VSTM tasks over a one-second epoch. For full details of these data sets the reader is referred to [9]. Both datasets consist of MCI patients at risk of AD and Controls performing a visual short-term memory task that assesses, via two conditions, memory for shapes and for shape-colour binding.

In the assessment of visual short-term memory (VSTM), two distinct tasks are employed [15]: a shape-only change detection task and a binding task. In the shape-only task, participants are presented with arrays featuring three different black shapes, while in the binding task, the arrays consist of three distinct shapes, each with a unique colour. Each trial in both tasks comprises three phases: an initial encoding period (lasting 500 ms) during which participants view a study array on the screen, followed by a short delay of 900 ms, and concluding with the test period. In the test period, a test array is displayed, and participants are tasked with determining whether the objects in the two arrays are identical or different. To prevent reliance on spatial cues, the positions of objects are randomized. Shapes and colours are randomly selected for each trial from sets of eight options. Notably, in 50 percent of the trials, both arrays feature identical objects. In the remaining 50 percent, changes occur: in the shape task, two shapes are substituted with new ones, while in the binding task, the colours of two shapes are interchanged. Participants commence with a practice session and subsequently complete 100 trials for each task. Importantly, the order in which they engage in the binding and shape tasks is systematically counterbalanced across participants, ensuring a comprehensive exploration of VSTM dynamics [9], [15].

Signal pre-processing was performed to get signals band-passed into Delta (0.01-4Hz), Theta (4-8Hz), Alpha (8-12Hz), Beta (12-30Hz) and Gamma (>30Hz) frequencies.

The network analysis was done using FAST Connectivity. We first computed the long-term connectivity over the whole epoch for each patient and control in each task using Pearson's correlation coefficient. We then applied Definition 1 to create our FAST filter of overall general VSTM task activity. A separate filter was created for the familial AD dataset and for the Sporadic AD dataset due to them being different experiments with different numbers and positioning of electrodes and different sampling frequencies. We then split the FAST Connectivity tensors into 10 0.1 second, non-overlapping temporal windows by averaging over smaller time windows to give us 10 matrices of FAST connectivity for each participant with a high temporal resolution.

F. Statistical Methods

We designate as a result of clinical interest as a given temporal window where there is a significant difference between patients and controls in the binding task and no significant difference in the shape task as this points to a specific binding deficit in AD. Non-parametric Wilcoxon rank-sum test are performed to assess for statistical significance between patients and controls. These are computed at each 0.1s temporal window between the vectors of mean network metrics for patients and controls at each temporal window. This is repeated for the mean edge weights and the mean weighted clustering coefficient values.The direction and size of the differences are calculated using Cohen's *d* effect size. In our experiments, a negative value would indicate a greater connectivity in the AD patients for the given VSTM task.

In order to account for the multiple comparisons we applied the Benjamini-Hochberg False Discovery Rate (FDR) correction to account for multiple temporal significance testing. This was done at the 10 and 5 percent level. While 5 percent is often held as the strict standard, the 10 percent level allows us to look for sensitivity pointing towards reproducibility across datasets– i.e. where one dataset passed FDR at a given timepoint at 5 percent and the other at 10 percent.

III. Results

A. FAST Connectivity Simulation

While there is a theoretical rationale to support our novel methodology, it is not a given that this follows through meaningfully in practice. Therefore, a simulation in a general case scenario is implemented to show the effectiveness of our method at picking up relevant Event-Related Potentials. This is tested across varying noise levels and the number of task trials. We performed a three-way comparison between the unfiltered node-function, individual GVD filters and our FAST filter.

The ERPs we chose to replicate are the N100 and P300. The N100 is characterized as a negative deflection in the EEG signal that occurs around 100 milliseconds after cognitive stimuli onset. The N100 typically peaks at around 100 milliseconds after onset and is usually attributed to early sensory processing in response to various stimuli. The N100 has been previously implicated in various neurological disorders such as Schizophrenia, Attention Deficit Hyperactivity Disorder (ADHD) and even Alzheimer's Disease. The P300 is characterized by a positive deflection in the EEG signal and usually occurs around 300 milliseconds post the presentation of stimuli. The P300 can be influenced by the given task the participant is involved in and is associated with the evaluation of the relevance of stimuli. The P300 has been heavily researched in AD [19], [20] and is associated with decision-making and working memory. We simulate these characteristics using the EEG model of Yeung et al.[17], [18].

Our aim is to evaluate the effectiveness of our methodology in detecting these simulated ERPs compared to a 'control' group where the ERPs are not present. We first use a Matrix of 1's, the same dimensions as our graph-variate signal, with 0's on the main diagonal to represent the unfiltered node function. We used the squared difference as our node function. Table 1 shows the log of the Wilcoxon rank-sum test p-values between the two groups of simulated participants at the time steps at 1000 trials with a very high level of external noise. Benjamini-Hochberg FDR correction is applied to account for multiple comparisons.

TABLE I: P-values over High External Noise Levels and 1000 Trials

Network Metric	**FAST Filtered**	**Unfiltered**
Clustering Coefficient	2.96×10^{-6}	0.6344
Edge Weight	1.699×10^{-7}	1

The goal of filtration with long-term stable connectivity in Graph Variate Signal Analysis is to improve the ability to detect important changes in activity in the presence of large amounts of noise. In order to show the benefit of the FAST filter compared to the unfiltered node function we added large amounts of white noise to the participants with the ERPs, essentially 'covering up' the ERPs to reach the point at which the unweighted node function can no longer efficiently pick out the simulated P300 and N100 ERPs but the FAST Filter can. Random Gaussian white noise is added randomly to each of the electrodes equally in the simulated setup (Note, we are adding random white noise which is distinct from the signal generated by the MATLAB functions that resemble the power spectrum of a typical human EEG recording). Figure 1 shows the p-values detected by the unfiltered modulus of the squared difference at the pre-determined P300 timestep. It is clear that it is unable to pick up any significant changes at this time point due to the external noise. The FAST filter however, picks up the significant differences at the time step with both the mean edge weights and clustering coefficient.

It is now evident that the unfiltered node function is failing to pick up the ERPs above a certain noise level limit. When we compared using individual filters for each participant, we found 'significant differences'; however, on further inspection, Figure 2 shows that the external noise results in the filters failing and every time-step is 'significantly different', whereas the global filter maintains the non-different and different time steps between both signal groups. Essentially the underlying stable support matrix is influencing the dynamic connectivity too much and thus detecting 'significant differences' in temporal windows when there are none simply due to differences

in the filters. The unbiased nature of the global filter in FAST connectivity helps overcome this issue.

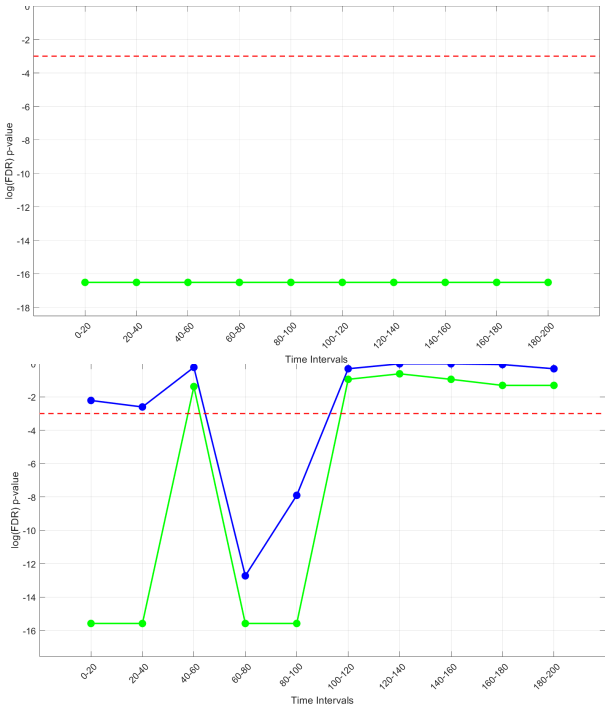

Fig. 1: Individual filters (Top) vs FAST Filters (Bottom), Blue for Clustering Coefficient,Green for Edge Weights

We found that, with the FAST filter, while sometimes a network metric might not pick out a significant result, in our experiments it never picked out spurious results as significant. I.e the false positive rate also appears to be very low. We have shown that the FAST filter outperforms the individual filters and the unweighted node function in a general simulated experimental setup similar to time-locked VSTM task comparisons.

We decided to test this more rigorously by varying levels of added Gaussian noise at different numbers of trials for each simulated participant EEG. The figure below shows the results of this as a heat-map matrix. We extracted the FDR corrected p-values at the P300 ERP time steps of interest (pre-determined to exist at these times-steps) thus we could compare the ability of the unfiltered and FAST filtered methods to pick out significant differences at these points. Lighter colours indicate more significant p-values while black represents a non-significant result. We tried trials ranging from 50-300 corresponding to typical real-life experiments where EEG signals are recorded.

We can see the FAST filter's robustness to increasing levels of noise with the edge weights picking up significant results at the correct time steps in almost all cases in the 100-300 trial range. At 50 trials, it still performs relatively well but there is a decreasing performance as more noise is added. The trend shows that as the number of trials increases the detection ability improves while increasing noise decreases this detection ability. The mean edge weights in the unfiltered case fail to detect these simulated ERPs in almost all levels

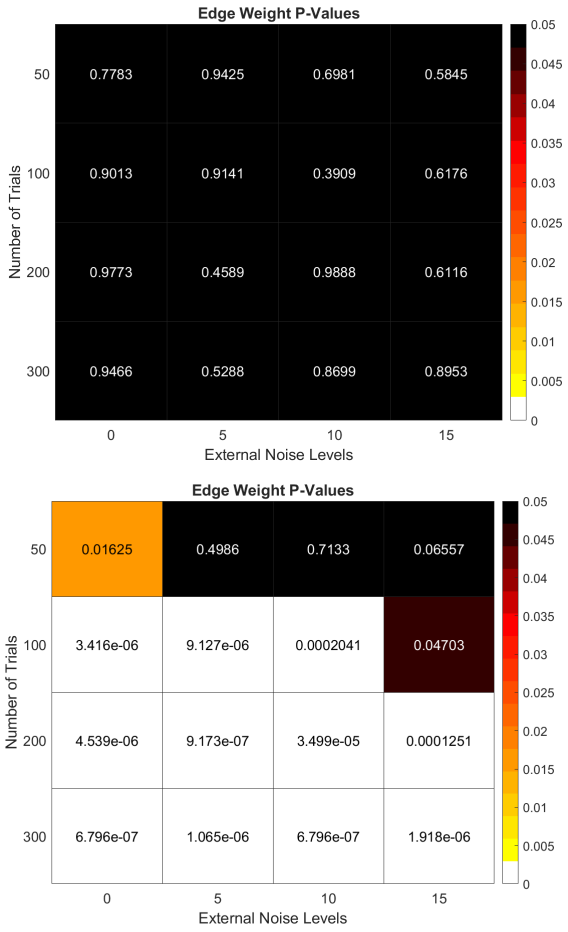

Fig. 2: The p-values at a pre-determined time-step of the simulated P300 at increasing levels of trial size and external Gaussian noise. FAST Filtered (Bottom) vs Unfiltered (Top).

of noise and trial sizes. Overall, the simulations are promising showing the clear benefit of the FAST filter compared to the unfiltered case and its evident robustness to noise.

Another important consideration in analyzing Dynamic functional connectivity in small temporal windows is the temporal resolution we can achieve while still maintaining robustness to noise. Previous methods depended heavily on the length of the sliding window in finding a trade-off between temporal resolution and robustness to noise. We decided to test the window length dependency of FAST connectivity by setting the number of windows equal to the sampling rate, i.e. maximum temporal resolution. Figure 3 shows the results of this at varying noise levels and trial sizes.

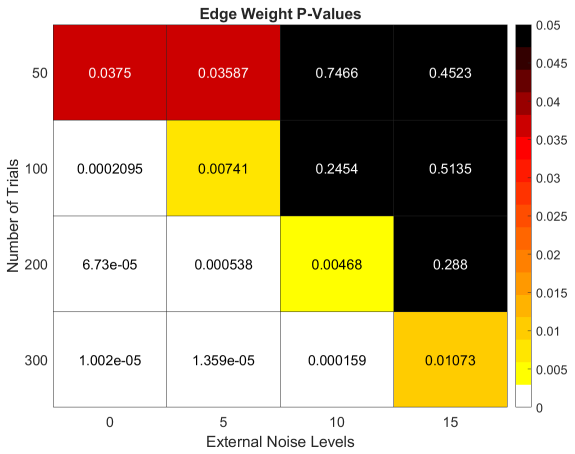

Fig. 3: Performance at maximum temporal resolution of FAST Filtered simulated EEG functional connectivity

The findings exhibit promise, revealing that despite a slight reduction in performance when utilizing maximum temporal resolution with 200 windows in contrast to 10 temporal windows, the decline is minimal and potentially insignificant, particularly with an optimal number of trials. This observation underscores the robustness of FAST connectivity in variance to window length variations, highlighting its comparative advantage over existing methodologies in capturing dynamic functional connectivity changes. Notably, at 200 trials, FAST connectivity demonstrates consistent detection across all noise levels. We note that at 50 trials, FAST connectivity can detect meaningful changes in functional connectivity; working memory tasks often require participants to engage in sustained cognitive effort, leading to potential cognitive fatigue, especially in prolonged experimental sessions. FAST connectivity shows potential to address this challenge by exploring the feasibility of achieving accurate ERP detection with a lower number of trials. Additionally, we should take into account economic considerations prevalent in low-income countries, where optimizing experimental protocols can significantly reduce costs associated with data acquisition and analysis.

B. Application to visual short-term memory binding in Alzheimer's disease

EEG micro-states are transient patterns of the electroencephalogram that occur in very small temporal windows and are considered to be related to the most basic of human neurological processes. They have been previously shown to be able to distinguish between neurological disorders such as schizophrenia based on these tiny temporal window differences where the overall functional connectivity of the brain may be very similar [21]. Recently, there has been significant interest in these EEG micro-states in neurological disorder diagnosis. Chu et al.[22] showed that combining graph metrics based on dynamic functional connectivity in small temporal windows with typical classification algorithms showed significantly improve performance in the early detection of Parkinson's Disease (PD), showing the discriminating ability of these EEG micro-states.

As mentioned earlier, we have a large number of options for the choice of bi-variate node function and long-term stable connectivity filter, but it is essential to prevent data dredging. From our simulations, we found that the FAST Correlation filter with the pairwise squared difference as the node-function to be the most effective combination at detecting relevant ERP's. Thus this will be the basis of our main results in our FAST Connectivity Analysis.

We used FAST connectivity matrices computed from participants in both VSTM tasks (shape and binding) to filter mean matrices of patients and controls in the binding VSTM task in both data sets. The temporal heat-maps of the theta band in the familial (top) and sporadic (bottom) dataset comparing controls (left) and patients (right) are shown below in Figure 4.

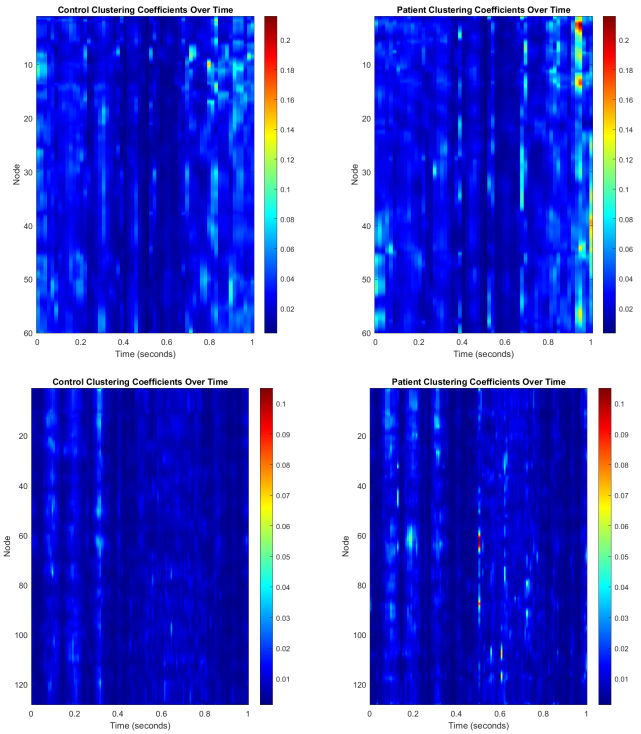

Fig. 4: Clustering Coefficient Heatmaps of mean FAST filtered control (left) and patient (right) matrices in the binding VSTM task in the familial and sporadic AD group in the theta band

It is interesting to note that in the FAST filtered mean matrix of patients against controls we see patches of increased clustering coefficient values in patients consistently across both datasets. Given the nature of the squared difference this could indicate points of increase in anti-correlative information or variation between signal pairs.

While the mean FAST filtered matrices do contain valuable information we do lose some transient information. We thus ran experiments for the Familial AD and Sporadic AD datasets separately with a single FAST filter computed from participants in both the shape and binding tasks for each frequency band. As mentioned in our statistical methods section we computed the mean clustering coefficient and edge weights of

each participant at ten disjoint temporal windows of the total one second epoch of interest and undertook non-parametric statistical testing between controls and patients to look for temporal windows where there is concurrently a significant difference between controls and patients in the binding task and no significant difference in the shape task. This exploits the proposed binding deficit established in [9]. Figure 5 shows the plots of the log of the p-values of the patients versus controls in shape and binding tasks for the familial AD dataset with values below the black dotted line indicating a significant difference. The scale is provided for the delta plot.

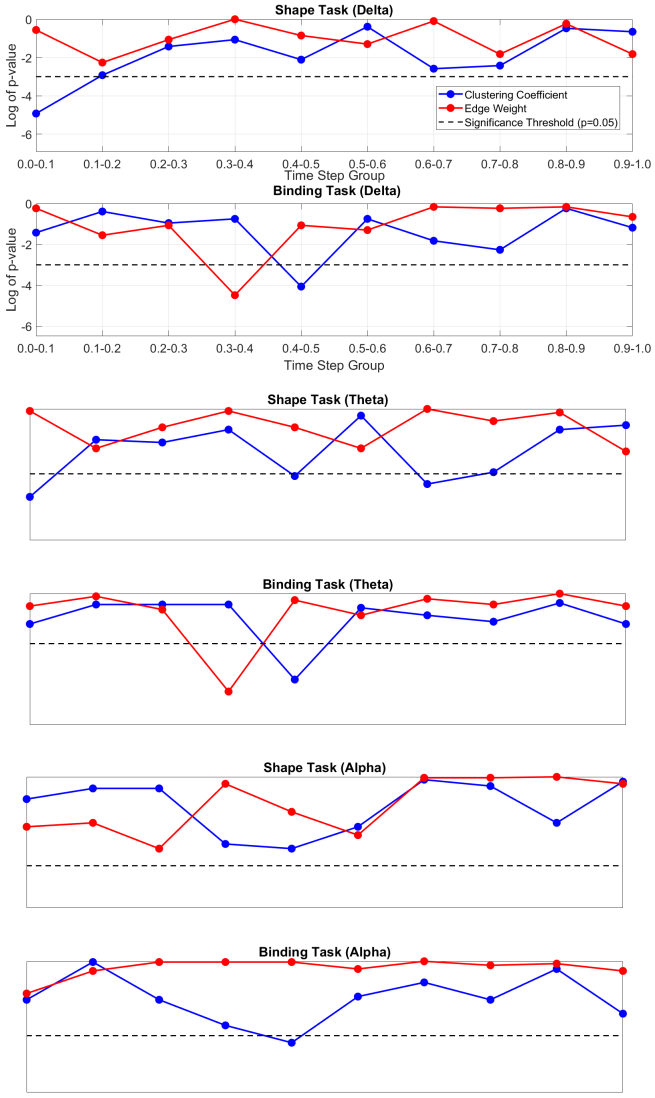

Fig. 5: FAST Connectivity Shape vs Binding task in delta(top),theta(middle) and alpha(bottom) bands for the Familial Group

The first thing we notice is that the behaviour of the delta and theta band in the binding task is nearly identical with significant results found at 0.3-0.4 seconds by the mean edge weights and 0.4-0.5 by the mean weighted clustering coefficient. We can see how having two different network metrics can aid the detection of clinically significant results. We see the shape tasks for these time steps are not significantly different thus these can be considered results of clinical interest as the specificity of binding deficits observed behaviorally are replicated here at a neural level. The binding task in the alpha band seems to show some behaviour similar to the theta and delta bands with a clinically interesting result at 0.4-0.5 seconds, however this would not pass FDR correction. The beta band seems to follow the same pattern in the 0.3-0.6 range with a dip towards the significance line in the binding task and movement away from it in the shape task. In light of volume conduction effects, the Gamma band was found to yield spurious significant results, consequently warranting its exclusion from our analysis. Overall, we notice a trend of clinically significant results in the 0.3-0.6 second range in the familial AD data-set, mainly in the lower frequency bands.

We now perform our FAST Connectivity Analysis on the Sporadic AD data set. Recall this is a completely independent dataset with a 128 electrode setup with 17 control and 13 (older) patients at high risk of Sporadic AD. The corresponding plots of the p-values between patients and controls for Shape and binding tasks over the one second epoch are given below. Note there may be a slight discrepancy between interval values due to the differing sampling rates, e.g. 0.3-0.4 seconds is actually 0.29-0.39 seconds.

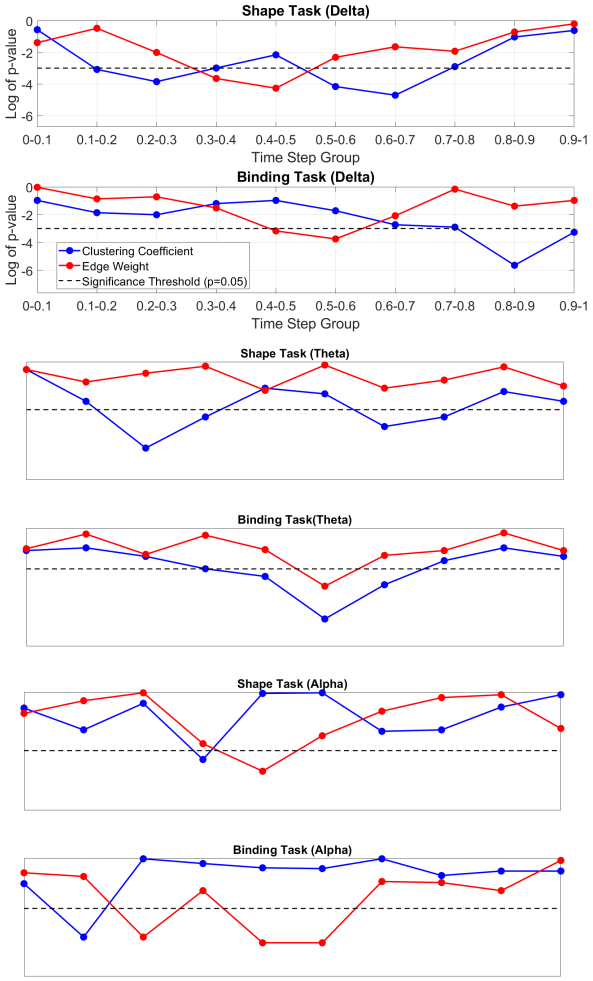

Fig. 6: FAST Connectivity Shape vs Binding task in delta(top),theta(middle) and alpha(bottom) bands for the Sporadic Group

We notice similar patterns in the lower frequency bands with the binding task in the delta and theta band following similar patterns in the mean edge weights and the network metrics picking up clinically interesting results in the theta band at 0.4-0.5 and 0.5-0.6 seconds. This is an overlap in the 0.3-0.6 second range with the familial AD data set. The delta band has a clinically interesting result at 0.5-0.6 seconds with the mean edge weights and a highly significant result at 0.8-0.9 seconds using the weighted clustering coefficient,this could be related to the emotion related Late Positive Potential (LPP). The LPP, characterized by a gradual positive shift in activation, typically manifests approximately 400-1000 ms following stimulus presentation. Its amplification has been linked to memory encoding and retention mechanisms [9]. Furthermore, it has been correlated with post-retrieval phases, such as decisional and evaluation processes which could be affected by AD.Again the overlap with the delta band in the familial AD group in the 0.3-0.6s range is seen. Moreover,the alpha band has clinically interesting results at 0.1-0.2 seconds with the weighted clustering coefficient and 0.2-0.3s and 0.5-0.6s with the mean edge weights. It seems the similarity to the theta band in the familial AD group is growing with the behaviour in the 0.3-0.6s range being much more prominent in the alpha band. The beta band has a significant result at the 0.4-0.5s time-step which is similar to the behaviour of the beta band in the familial AD data-set (dip towards significance line in binding task, movement away in the shape task). Overall, there are consistent overlapping results of clinical interest in the 0.3-0.6s temporal range.

We then applied FDR correction at the 10 percent and 5 percent level to account for multiple comparisons. Table 2 below shows the time intervals at which there is a significant difference between controls and patients in the binding task and not in the shape task.

TABLE II: FDR Corrected Data sets. The underlined text represents the Binding p-value below 0.05. Bold font indicates ranges in the first 300ms of the P300.

Freq. Band	Range	Binding p-value	Binding Effect Size
Familial Theta	**0.3-0.4**, **0.4-0.5**	0.028, 0.058	1.60, -1.12
Sporadic Delta	0.8-0.9	0.035	-0.55
Sporadic Theta	**0.5-0.6**	0.013	-1.19
Sporadic Alpha	0.1-0.2, 0.2-0.3, **0.5-0.6**	0.09, 0.03, 0.03	-0.88, -1.17, -1.10

Table 2 shows results that are of clinical interest after applying FDR correction at the 5 and 10 percent level. The main results that survive FDR correction are 0.3-0.6 range results in the lower frequency bands. There are overlapping significant results in the 0.3-0.6s range in the familial and sporadic AD data sets. The 0.3-0.6 results in the Sporadic AD alpha band pass FDR correction, thus bringing evidence of an ageing interplay between the alpha band frequency in the older sporadic AD patient group mimicking the behaviour of the Theta band in the younger familial AD patient group. The binding task effect sizes are all consistently greater in the patient group suggesting increased FAST connectivity in Alzheimer's patients during binding VSTM tasks. This correlates to our time series plot of the FAST filtered mean patient and control matrices. The 0.3-0.4 range in the familial theta band shows greater squared difference values in controls with a rapid switch to greater values in patients in the next time step. We conjecture that this could be due to the oscillating behaviour of Event Related Potentials.

IV. Discussion

Our simulations showed the benefit of FAST Connectivity compared to standard connectivity measures in picking up ERPs between participants with and without the discriminating ERP. We have provided a high temporal resolution method that is robust to noise in small temporal windows while being very invariant to the window length. Thus we achieve a better trade-off of noise robustness and temporal resolution compared to existing methods[10].

After applying these results to our two independent sporadic AD and Familial AD data sets, we found consistent overlapping clinically significant results in the 0.3-0.6 second range. This corresponds to the P300 range previously implicated in Alzheimer's Disease [19]. Exploiting the binding deficit proposed by Pietto et al.[9] we have found evidence of an increase in anti-correlative activity or signal variation in Alzheimer's patients in the P300 range during binding VSTM tasks and not in Shape VSTM tasks. This supports the binding task deficit as a potential biomarker for AD. FAST Connectivity performed well in negating spurious connections and emphasizing the important ones in the P300 range. Theta band irregularities have been well-researched to be linked to MCI due to Alzheimer's disease[23]. While the slowing of the alpha band is an indicator of progressing AD [24]. The Alpha and Theta band 'shifts' could be of clinical significance as the two independent datasets differ by age; thus the alpha band in the older Sporadic AD data set mimicking the behaviour of the Theta band in the younger Familial AD data set in the P300 range could provide an indicator for the progression of the disease from MCI to more severe full-on dementia. Alternatively, this frequency shift may be signaling age-related compensatory neural mechanisms which have been previously reported during memory tasks performed in the fMRI scanner [25].

Given our low sample size, we acknowledge the effectiveness of FAST Connectivity at picking out clinically significant results, especially given we have more controls in the sporadic AD data set. After rigorously performing simulations showing the effectiveness of our novel methodology, our application of it to the two data sets has provided potential biomarkers for the early detection of Alzheimer's Disease and the progression of MCI to Dementia. Given the non-invasive nature of EEG signal Analysis combined with the low computational cost of using GVD connectivity with a relatively small number of patients, we see the potential for this method to be used in

the diagnosis of Alzheimer's disease for low-income individuals.We also see potential for accurate ERP detection at a lower number of trials, which could address the cognitive fatigue of participants in these working memory-based tasks. This could also reduce the cost, especially in low-income countries such as Latin America.

An obvious application of FAST connectivity or similar methods would be in Brain Computer Interfaces (BCI).The ability to exploit discriminating information in real time from cheap, non-invasive EEG signals provides an avenue for an realistic, widely accessible BCI. While we are still far away from real-time detection, FAST connectivity, with its high in-variance to window length changes and performance at temporal resolution, shows potential for this one day being a possibility. Given recent advances in network based BCIs [26] and the proven importance of functional connectivity dynamics in the performance of BCIs [27] this would be a worthwhile avenue to explore.

Given the provision of more data, we could have drawn more validity to our clinical results. However they are still promising. Further work should focus on the optimization of the bi-variate node function and the Long-term Stable connectivity filter, focusing on interpretability and robustness against noise. In particular, it would be beneficial to look into the effect of certain node functions emphasizing specific signal properties such as anti-correlative information seen with the squared difference.The diagnosis of neurological disorders in psychiatry is an area of uncertainty due to the overlap between disorders. GVD Connectivity provides potential in the analysis of EEG signals to provide a more quantitative judgement on the nature of the neurological disorder. Machine Learning can be implemented on the network metrics of GVD connectivity due to the high temporal resolution of the metrics, this could add important transient information to Machine learning algorithms significantly improving performance akin to the wavelet transform shown to increase classification accuracy of neurological disorders by adding transient information[28].

While the results show the promise of this new methodology, it is worthwhile reflecting on where it may fail. We have already mentioned that it would not be suitable for picking up transient functional activity among connections which are otherwise independent, and so having low long-term connectivity. Additionally, since the FAST filter is based on long-term connectivity, it should foremost be applied to singular cognitive processes. This means that it may not be suitable to apply to instances where there are expected changes in the cognitive function of a task, for example.

V. Conclusion

We have introduced FAST connectivity, a novel algorithm building on Graph Variate Dynamic (GVD) Connectivity that leverages a single global filter computed from both groups of participants in a given EEG paradigm. We have shown, in controlled simulations on synthetic data, that the method outperforms previous Graph-Variate methods in detecting subtle differences in small temporal windows between groups of participants with and without a simulated ERP in noisy conditions. We have also shown the lower dependence on window length of the method, providing an alternative to existing sliding window methods. Of notable interest is the fact there is still relatively good performance when the window length is equal to the sampling rate allowing us to potentially detect changes in temporal windows at a very granular level. Applying FAST connectivity to two independent cohorts of Sporadic and Familial Alzheimer's Disease patients engaged in VSTM tasks, we found significant differences between groups in the 0.3-0.6 second range in the binding task but not in the shape task, previous studies corresponds this to the P300 ERP range . This was more prominent in the lower frequency bands, in particular, the theta band. Corresponding with previous studies on the binding deficit and the role of the theta band in Alzheimer's disease . Future work should aim to focus on further studying the properties of the Global filter, such as the Graph Laplacian eigenvalues in order to analytically understand its noise reduction and important connection promotion effects. Different node functions based on the structure of the graph signal data should also be explored.

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