Spectral graph modeling reveals global slowing of neurophysiological network transmission in Alzheimer’s disease

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Article

Keywords: brain activity, Alzheimer's disease, magnetoencephalography, spectral graph theory, cognitive decline
Additional Declarations: Yes there is potential Competing Interest. Bruce Miller serves as Medical Director for the John Douglas French Foundation; Scientific Director for the Tau Consortium; Director/Medical Advisory Board of the Larry L. Hillblom Foundation; and Scientific Advisory Board Member for the National Institute for Health Research Cambridge Biomedical Research Centre and its subunit, the Biomedical Research Unit in Dementia, UK
Spectral graph modeling reveals global slowing of neurophysiological network transmission in Alzheimer’s disease

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Abstract

Alzheimer’s disease (AD) is the most common form of dementia, progressively impairing memory and cognition. While neuroimaging studies have revealed functional abnormalities in AD, how these relate to aberrant neuronal circuit mechanisms remains unclear. We employed a spectral graph-theory model (SGM) to identify abnormal biophysical markers of neuronal activity in AD. SGM is an analytic model that describes how long-range fiber projections in the brain mediate excitatory and inhibitory activity of local neuronal subpopulations. We estimated SGM parameters that captured the regional power spectra obtained from magnetoencephalography imaging of a well-characterized population of patients with AD and controls. The long-range excitatory time constant was the most important feature for the accurate classification of AD and controls and was associated with global cognitive deficits in AD. These results indicate that a global impairment in the long-range excitatory neurons might be a sufficient factor underlying spatiotemporal alterations of neuronal activity in AD.

Keywords: brain activity, Alzheimer’s disease, magnetoencephalography, spectral graph theory, cognitive decline

1 Introduction

Alzheimer’s disease (AD) is the most common form of dementia, progressively impairing the cognition and behavior of the affected individual. It has been proposed that the effect of AD neurodegeneration on cortical neuronal networks is partially reflected by the abnormal mechanisms of cortical neural synchronization and coupling [1]. Neural synchronization refers to the simultaneous activity of neuronal groups in the brain. Repetitive spiking activities of neural populations form an oscillatory behavior at frequencies ranging from slow delta waves to fast gamma waves. We may distinguish between two types of synchrony: local synchrony,
typically measured via the power spectral density (PSD) of the electrophysiological signal at the regional level; and long-range synchrony, deduced as the pair-wise coherence between signals originating at different locations - also referred to as functional connectivity or FC. Neurodegeneration is thought to disrupt both local and long-range synchronization [2, 1, 3]. These deficits are present long before the onset of clinical symptoms, worsen as the symptoms occur and progress, and may play a role in disease manifestation [4]. It is therefore important to understand how the pathology-induced neurodegeneration in AD leads to disruption in large-scale synchrony within and between brain regions, and how they then lead to cognitive impairment.

Functional neuroimaging studies are indispensable for understanding the role of aberrant synchrony in AD, and of its functional consequences. Resting-state functional MRI (fMRI), which measures the slow fluctuations of blood oxygenation signal in the brain as a proxy for neural activity [5], readily gives the low-frequency FC. Leveraging graph-theoretic analyses, many studies now routinely describe the alterations in FC during the course of AD pathophysiology [6]. Graph theoretic statistics of FC from resting-state fMRI however have shown inconsistent differences between AD patients and control samples [7, 8], perhaps due to fMRI’s limited ability to capture fast temporal scales of neuronal activity [9].

In contrast, electrophysiological techniques such as electro- or magneto-encephalography (E/MEG) can capture temporal activity scales with millisecond precision. FC features extracted from MEG activity were demonstrated as an early biomarker of AD burden [10–12] and showed that the graph metrics between AD and control samples vary across different frequency bands. Other studies have demonstrated aberrant FC signatures in AD [13–18]. Degradation of callosal fiber integrity was accompanied by loss of brain interhemispheric functional connectivity characterized by increased delta-band, and decreased alpha-band, path length using FC obtained from EEG recordings [19], suggesting that global FC measures can reflect fiber disconnectivity in AD. Significant differences were observed in various coherence-based measures of long-range synchrony in AD compared to control subjects [1]. There is also now substantial evidence that local synchrony is aberrant in AD. EEG analysis revealed that the relative PSD of AD patients is significantly increased in delta- and theta-, while reduced in alpha-band [2]. A recent MEG study conducted by our group suggested striking shifts in the power spectra of neural activity in AD patients compared to healthy subjects, the most prominent being a shift of power from the normally-dominant alpha band to the lower delta-theta bands [18]. We further showed that the shift in MEG spectra in AD is regionally-specific and accounted for by altered excitatory and inhibitory parameters which are well-predicted by local Aβ and tau concentration as measured by PET imaging - giving a direct connection to how pathology alters the excitatory-inhibitory balance in AD [18].

These data have naturally led to a search for underlying neural mechanisms whose impairment in AD might help explain these electrophysiological alterations in AD. A beginning in this direction was reported in our recent study [18], where each regional PSD was fitted by a localized and linearized neural mass model. While such local models can powerfully reveal local alterations in neural systems, e.g. excitatory/inhibitory imbalances, they did not consider the anatomic network structure of the brain. Indeed, the anatomic network enables short- and long-range communication between cortical neurons, and through regenerative feedback, can support spontaneous functional organization of synchronized neuronal firing at different timescales and generates oscillations of different frequencies [20]. Further, a local disruption of neural systems is not the only possible factor at play in AD. It is well known that AD is accompanied by global (i.e. brain-wide) changes in electrophysiological processes, e.g. slower axonal conductance speeds [21], less efficient signal transfer due to axonal swelling and demyelination [22], higher noise and less efficient synaptic signaling [23], across the brain. All these global effects have the potential to alter the spectral profile as well as the FC of neural activity measured on MEG.

Therefore there remains a pressing need to apply parsimonious models of brain activity that are applicable
at the whole-network level while accommodating global, region-invariant parameters, and to understand whether such models can recreate AD-induced spectral shifts. In these efforts, it is frequently necessary to employ mathematical models that codify the effect of abnormal changes in biophysical mechanisms on neuronal activity. Computational investigations, frequently employing coupled neural mass models, are becoming popular in AD and dementia [24], yet their practical impact has been limited by their non-linearity, long simulation times, high dimensionality, and intractable parameter inference.

In order to address these challenges, in this paper we introduce a rigorous model-based assessment of the role of global, mechanistic alterations in AD electrophysiology, especially their coupling via the structural connectome. This approach, therefore, seeks to complement our prior study on uncoupled locally-varying neural masses [18]. The mathematical model we employed is the spectral graph theory-based model (SGM) to identify abnormal biophysical markers of neuronal activity in AD. SGM is a linearized and analytic (i.e. closed-form) model that describes the activity of excitatory and inhibitory neuronal populations in different brain regions, coupled and mediated by the long-range white matter structural wiring [25, 26]. SGM is parameterized by a small set of 7 global, regionally-invariant parameters, and relies on the connectome to achieve regional diversity. It was previously successful in capturing the resting state MEG spectral signatures across all brain regions of healthy subjects [25, 26]. Due to its parsimony, SGM yields easy and tractable model inference and hence is an ideal tool for inferring underlying biophysical correlates of AD-related MEG alterations. We use SGM to specifically test the hypothesis that the model’s parameters that control long-range synchrony via its coupling with the anatomical network will be impaired in AD and could provide a parsimonious account for cognitive decline.

We performed a thorough parameter inference of the SGM on individual subjects’ MEG recordings from a well-characterized clinical population of AD patients and a cohort of age-matched controls studied previously [17]. Detailed statistical analysis on the fitted parameters was conducted in order to assess group-level differences in global mechanisms of neural activity. We found that while AD and healthy groups showed many subtle differences in several global SGM parameters, only one stood out and was responsible for the majority of group-wise changes. Indeed, patients with AD have significantly elevated long-range excitatory neuronal time constant compared to controls. This time constant is also the most important feature for the accurate classification of AD from controls and is strongly associated with the global measure of cognition. Intriguingly, the SGM can be decomposed into a small set of eigenmodes of the network, in a striking resemblance with a similar eigendecomposition that we previously used to explain the spread of pathology on the brain [27]. Our results clearly implicate altered long-range excitatory time constant as a key hallmark of AD-related function. To our knowledge, this is the first report of a single global parameter change that can reliably produce spectral shifts from healthy to AD brains. Our study is therefore an intriguing counterpoint to prior studies highlighting the localized effects of AD on brain activity. Potentially, this fills a key missing link between AD pathology and downstream altered activity and cognitive deficits.

2 Results

SGM provides a closed-form solution of the steady-state frequency response of different brain regions. Here, we use a Desikan-Killiany parcellation scheme [28] to estimate the brain regions. The SGM is characterized by 7 parameters, which are either global or local but spatially-invariant. These parameters include the spatially-invariant local synchrony-related time constants $\tau_e, \tau_i$ and spatially-invariant but local neural gains $g_{ei}, g_{ii}$ at the mesoscopic scale for both excitatory and inhibitory neuronal subpopulations; as well as a global excitatory time constant $\tau_G$ at the macroscopic scale representing the long-range network connections, global coupling constant $\alpha$, and speed of transmission of signals among regions $v$. Each region is assumed to
consist of local excitatory and inhibitory neuronal subpopulations that interact with each other and regulate the macroscopic long-range excitatory neuronal populations. The macroscopic long-range populations are assumed to be connected to each other via the structural connectome. Here, we use a template structural connectome from the Human Connectome Project (HCP). Hence the model entails no features that may change from region to region, except of course features from the heterogeneously connected anatomical network.

To infer the SGM parameters, we fit SGM output to the frequency spectra obtained from MEG for healthy controls and AD subjects. A workflow is shown in Fig. 1.

2.1 SGM reliably reproduces the patterns of spectral power density.

The predicted spectra from SGM reliably captured the empirical MEG spectra from patients with AD and age-matched controls (Fig. 2A; The mean (std) spectral correlations were 0.72 (0.08) and 0.78 (0.09) for controls and AD, respectively). Compared to age-matched controls, patients with AD showed a reduced alpha peak and increased spectral power within the low-frequency delta-theta range (1-7 Hz), in their empirical spectral recording from MEG. This characteristic spectral change is clearly replicated in the predicted spectra derived from SGM. The spatial distribution of spectral power density of the alpha band, as expected, showed a postero-anterior distribution in both controls and patients. The spatial patterns of the predicted spectra from SGM reproduced this postero-anterior distribution with high fidelity (Fig. 2B; the mean (std) spatial correlations were 0.60 (0.09) and 0.66 (0.09) for controls and AD, respectively)

2.2 AD patients have altered network time constants and neural gains.

Next, we compared the network parameters derived from the SGM between patients with AD and age-matched controls. Recall that these parameters are either global or local but assumed spatially-invariant. Using a general linear model with age included as a covariate, we found that patients with AD have significantly elevated long-range excitatory time constant ($\tau_G$; controls mean = 7.50, confidence interval = (6.32, 8.68), AD mean = 13.90, confidence interval = (12.72, 15.09), Cohen’s D effect size = 1.16), mesoscopic excitatory time constant, ($\tau_e$; controls mean = 11.88, confidence interval = (10.36, 13.41), AD mean = 15.01, confidence interval = (13.48, 16.53), Cohen’s D effect size = 0.41) and mesoscopic inhibitory neural gain ($g_{ii}$; controls mean = 0.26, confidence interval = (0.16, 0.36), AD mean = 0.46, confidence interval = (0.36, 0.56), Cohen’s D effect size = 0.42; Fig. 3A, B, and C). The highest effect size among the parameter comparisons was found in $\tau_G$ between AD and controls. Collectively these results indicate that while global network parameters are altered in AD, long-range excitatory connections may reflect such changes with greater sensitivity than other parameters.

2.3 Altered global network parameters can distinguish between AD and controls with high accuracy.

Next, we examined the sensitivity and specificity of altered global network parameters to distinguish between patients with AD and controls. To this end, we trained and tested a random forest classifier including the model parameters and age as the classifier features. The average AUC of the ROC curves from the testing folds is 0.85, with a standard deviation of 0.02 (Fig. 3D). The other classification metrics included: accuracy = 0.78, precision = 0.79, recall score = 0.75, and f1 score = 0.77, on average. We also obtained the feature importance score of the features used in training the model, shown in Fig. 3E. The time constant $\tau_G$ was the most important feature in classifying AD versus controls. Collectively, these results indicate that
Figure 1: SGM models excitatory and inhibitory neuronal subpopulation signals that influence the long-range excitatory signals. The long-range signals are connected to each other via the structural connectome, and these signals transmit with a fixed conduction speed. SGM provides a closed-form solution in the frequency domain. This is compared to the frequency spectra obtained from MEG for inferring the SGM model parameters.
Figure 2: **A:** Comparison of empirical (left) and SGM (right) frequency spectra. Lighter lines correspond to frequency spectra for each brain region and subject. The darker lines correspond to the spectra averaged over all regions and subjects, separately for AD and controls. 

**B:** Spatial distribution of the empirical (left) and SGM (right) alpha frequency band, for subjects with mean spatial correlations in controls (top) and AD (bottom). The color scale of each spatial distribution was chosen based on their dynamic range.
Figure 3: A, B, C: Statistical significance testing of difference in model parameters between AD and controls, with age as a covariate. Distribution of A: macroscopic parameters $\tau_G$ (long-range excitatory time constant), $v$ (speed), and $\alpha$ (coupling constant); B: mesoscopic time constants $\tau_e$ (excitatory) and $\tau_i$ (inhibitory); and C: mesoscopic neural gains $g_{ii}$ (inhibitory gain) and $g_{ei}$ (gain of signals from the coupling between excitatory and inhibitory neurons). P-values are reported after correcting for multiple testing using a Bonferroni correction. $^\ast$: $p < 0.05$, $^\ast \ast \ast$: $p < 0.001$. D, E: Classification of AD vs controls with a random forest classifier with SGM parameters and age as features of the classifier. D: ROC curve for classification of AD versus controls. E: Feature importance plot of SGM parameters. F: Spectral correlations when optimizing for only certain model parameters while keeping the others fixed at the average of the optimized model parameters of both AD and controls. “None” implies that all the model parameters were fixed at the average. The second point on the x-axis with the label $\tau_G$ implies that only $\tau_G$ was allowed to be optimized while the other model parameters were fixed at the average values. The third point on the x-axis with the label $\tau_e$ implies that both $\tau_G$ and $\tau_e$ were allowed to be optimized while keeping the other model parameters fixed at the average values. All the subsequent points on the x-axis correspond to similarly including more model parameters in optimization, based on their importance in the classification of AD vs controls.
altered global network parameters are reliable indices to identify patients with AD from their age-matched counterparts and that long-range excitatory connections are the most sensitive indicators of AD-related global network deficits.

2.4 Minimal set of altered model parameters capture the empirical spectra.

In order to assess the importance of model parameters in capturing the empirical spectra, we evaluated the spectral and spatial correlations after optimizing for certain model parameters, based on their importance from Fig. 3E, while keeping the remaining model parameters as the average of all the optimized model parameters for AD and controls together. First, we evaluated the correlations when none of the model parameters are optimized for and are all the average of the optimal parameters obtained previously. Next, we optimized only for $\tau_G$ while keeping all the other model parameters fixed since $\tau_G$ was the most important parameter in the classification of AD vs controls. Subsequently, we optimized for both $\tau_G$ and $\tau_e$ while keeping the remaining model parameters fixed since $\tau_e$ was the second most important feature in classification. We repeated this procedure till we included all the model parameters for optimization. The spectral correlations from this evaluation are reported in Fig. 3F. As seen in the figure, we see a sharp increase when $\tau_G$ is allowed to vary while keeping the other model parameters fixed. Upon including the subsequent model parameters, we do not see a substantial increase in the spectral correlation. This result strengthens our prior observation on the importance of $\tau_G$ in differentiating AD from controls. Note that we did not see any substantial difference in the spatial correlations.

2.5 Altered long-range excitatory connections are correlated with global cognitive deficits in patients with AD.

To investigate the association between altered global network parameters and cognitive deficits in patients with AD, we examined the correlations between $\tau_G$, $\tau_e$, and $g_{ii}$ with global cognitive decline measured by Mini Mental State Exam (MMSE), and overall disease severity measured by clinical dementia rating sum of boxes (CDR), in patients with AD. We first tested for univariate associations between the model parameters and MMSE and CDR separately, using linear regression. After adjusting for multiple testing (Bonferroni), $\tau_G$ showed significant negative associations with MMSE (Fig. 4A) where higher $\tau_G$ predicted greater cognitive deficits in MMSE. Next, we tested for the association between $\tau_G$ and MMSE including $\tau_e$, $g_{ii}$, and age as covariates in a multivariate linear regression model. This multivariate analysis also showed a significant negative association between $\tau_G$ and MMSE only ($p = 0.007$ for the association between $\tau_G$ and MMSE, model $r = 0.402$, model adjusted $r^2 = 0.121$, $F = 3.961$). Similar to the univariate results, none of the parameters were significantly associated with CDR in a multivariate regression model after adjusting for multiple testing.

3 Discussion

The goal of this study was to employ biophysical model-based reasoning to uncover AD-related changes in the spectral characteristics of neuronal activity. We leveraged the high spatiotemporal resolution of MEG to derive characteristics of altered spectral signatures and mapped them onto mesoscopic and macroscopic parameters of a computational model of brain activity. Our chosen model was the spectral graph model (SGM), which is ideally suited for this exploration since it is linear, easy to evaluate, tractable to infer, gives power spectra directly, and most importantly, serves as a computational link between structure and
function in the brain. We were able to demonstrate that global mechanisms of neural activity are significantly altered in patients with AD. Specifically, we found that the characteristic time constant associated with long-range excitatory connections is the most sensitive biophysical property that mediates altered global network dynamics in patients with AD. This parameter not only recapitulates the spectral shifts observed in AD but is also correlated with global cognitive deficits in patients with AD. This and other global network parameters were excellent computational disease biomarkers since they could accurately classify AD versus controls with a random forest classifier. The current investigation also demonstrates the ability of a model which uses global, spatially-invariant parameters, and the structural connectome as the basis for signal communication to successfully capture the spectral signatures in both degree and distribution.

To our knowledge, this is the first report of a single global parameter change that can reliably produce spectral and regional shifts from healthy to AD brains and is also correlated with cognitive deficits. Our findings provide critical insights about potential mechanistic links between abnormal neural oscillations and cellular correlates of impaired neuronal activity in AD. Because such insights from non-invasive neuroimaging data in clinical populations can only be obtained through a combination of mathematical modeling, our study fills a key missing link between impaired long-range excitatory connections and cognitive deficits in patients with AD.

3.1 Biophysical significance of highlighted model parameters

The parameters that were differentially distributed in AD were the excitatory time constants $\tau_G$ and $\tau_e$, and inhibitory neural gain $g_{ii}$. Each parameter has a distinct biophysical meaning, and clear implications in AD pathophysiology, as discussed below.

Macroscopic time constant. The most important differential parameter in our work was the long-range excitatory time constant $\tau_G$, which was substantially higher in AD, was found capable of recapitulating the spectral shift seen in AD patients, and was the most important feature in classifying AD from controls. Higher $\tau_G$ in AD indicates the slowing of long-range brain-wide communication of neural activity, implicating primarily the large layer-specific pyramidal glutamatergic neurons [29]. These pyramidal neurons are well-known to be selectively vulnerable in AD and indeed many other neurodegenerative diseases [30]. In addition, this result is in concordance with a recent study demonstrating long-range axonal connectivity disruption in
Intriguingly, we report that $\tau_G$ is also associated with global cognitive deficits in patients. This implicates impairment in the synaptic processing of macroscopic long-range excitatory neurons, a potential factor in the elongation of $\tau_G$, as a key marker of AD. Our recent study showed that alpha hyposynchrony is correlated with the degree of global cognitive dysfunction in patients with AD [17]. While such associations can be obtained using neuroimaging data directly, here we were able to identify a specific biophysically grounded parameter, $\tau_G$, that can potentially explain the biological relationship. Linking biophysical processes to clinical scales has historically been extremely challenging for conventional machine learning approaches due to the mismatch in dimensionality between input features (thousands) and output features (a handful of clinical measures). Increased long-range time constant in AD, capable of recapitulating the spectral shifts in AD and correlated with MMSE, therefore, may be the first report of a single biophysical correlate accounting for clinical deficits in patients with AD.

**Mesoscopic excitatory time constant.** The SGM model incorporates two additional neural time constants: a lumped mass of local (mesoscopic) excitatory and a mass of local inhibitory neural populations. Local excitatory-inhibitory imbalances in AD have been demonstrated in numerous basic science studies [32]. Consistent with our previous investigation [18], we also found that excitatory and inhibitory neural parameters within local ensembles are abnormal in patients with AD, although their effect sizes were small compared to the long-range time constant parameter. Among the local parameters, the strongest relationship was found with the mesoscopic excitatory time constant $\tau_e$, which was higher in AD subjects than in controls, consistent with our previous findings. While higher $\tau_e$ implies the slowing of the short-range excitatory signals at the mesoscopic level, we previously demonstrated that increased $\tau_e$ is distinctly associated with tau accumulation in AD. The relationship between spatially invariant long-range excitatory time constant and regional tau accumulation in AD remains to be elucidated.

**Inhibitory neural gain** We also found that the inhibitory neural gain $g_{ii}$ is higher in AD subjects than in controls. Neural gains incorporate the gain in internal recurrent signals due to local connectivities within a specific region. Higher $g_{ii}$ implies a higher gain of the inhibitory neural signals at the mesoscopic level. Alteration in the neural gain term indicates a neuronal excitatory-inhibitory imbalance; such an imbalance has been reported in various preclinical AD models [33, 15, 34, 35]. Overall increased inhibitory gain was found in epilepsy [36], while the local subpopulation estimates in AD showed reductions as seen in our previous study [18]. This discrepancy requires further study in the future.

### 3.2 Spatially invariant network effects

Due to the highly specific spatial topography of AD pathology [6], prior literature has broadly focused on the neural correlates of local circuits as the primary means of describing observed electrophysiological data [32]. In a recent study, we implemented a local linearized neural mass model of activity, and fit it to the regional MEG spectra in AD patients. We used this model, with spatially-varying neural masses and their parameters, to test the hypothesis that local changes in model parameters could recapitulate regional spectral shifts in AD patients. We also reported profound alterations in local excitatory to inhibitory parameters that attribute to regional distributions of tau and amyloid-$\beta$ PET imaging in AD patients [18]. The current study addresses a very different hypothesis: that observed alterations in MEG in AD patients may be explained by **global** changes in the network, as compared to spatially-varying changes in local neural masses. The SGM model used here combines local excitatory and inhibitory neural masses with a macroscopic connectome-based network of excitatory connections. Therefore in this study, we have kept all mesoscopic (local) parameters identical across the entire brain and only allowed them to change globally.

While the two hypotheses on spatially variant versus invariant effects in AD are not mutually exclusive, our key contribution here is to show that global changes are fully sufficient in their own right. A previous
modeling study using coupled neural masses also found differences in both coupling and local circuits [24]. Even though AD may induce both local and global changes, it is possible that the latter may dominate, as previously noted from a modeling perspective [37–41] and from our results indicating macroscopic $\tau_G$ as the most important parameter. Heterogeneity of the Amyloid-$\beta$ load was previously found to be essential to simulate the slowing of rhythm [42], but we have demonstrated that spatial variations of any kind in our model are not needed to capture the spectral and alpha-band spatial patterns. This certainly leaves room for the possibility that the SGM will be enriched by including the spatial patterns of Amyloid-$\beta$ and tau. Future explorations of the respective contributions of local versus global network changes in AD will be critical.

This local versus global distinction also means that our current results are not directly comparable to prior spatially-variable modeling results. Both the macroscopic ($\tau_G$) and the mesoscopic ($\tau_e$ and $g_{ii}$) parameters in our SGM model showed significant group differences, but we did not reproduce other local changes reported, e.g., in [18]. Nevertheless, $\tau_e$ being higher in AD in both the local as well as global study indicate a common underlying mechanism involving excitatory neuronal subpopulations at both local and global level in AD. Our local study had found a reduced inhibitory gain $g_{ii}$ in AD patients compared to controls [18], whereas the current global study did not; possibly because the current $g_{ii}$ is regionally-invariant, and was not uniquely estimated for each region’s local inhibitory subpopulation.

**3.3 Intriguing link to eigenmodes responsible for pathology transmission**

It was previously shown by our group that the eigendecomposition of the graph Laplacian can be used to describe the spread of pathology as it ramifies within the brain’s anatomic connectivity network. It was demonstrated that only the eigenmodes corresponding to the lowest eigenvalues - named “persistent modes” are involved in AD pathology progression [27]. Since any aberration in long-range synchrony explored here must arise from the underlying progression of pathology in the AD brain, it is expected that the same or similar eigenmodes responsible for pathology progression may also be involved in aberrant FC. The SGM too can be decomposed into a small set of eigenmodes (see Eq 1). Remarkably, it was recently shown by our group that the lowest few eigenmodes of the SGM capture a large portion of the spatial distribution of alpha-band power [26], and are also important in explaining low-frequency FC from BOLD fMRI [43]. This striking resemblance of eigenmodes of both pathological and electrophysiological processes establishes a conceptual bridge that has been hitherto unknown.

**3.4 Relationship to previous modeling works**

Even though no mathematical model can capture the complex brain structure-function relationship completely, many can aid in identifying mechanisms that cannot be inferred with neuroimaging data alone. Indeed, various model-based markers of AD have also been shown in the past. For example, the Virtual Brain Modeling platform has been used to estimate local and global parameters of a neural mass model for fMRI and to subsequently differentiate between AD and controls [24]. While the literature on fMRI studies in AD is vast, comparable depth is lacking in the use of higher frequency data like MEG. In our work, we focus on MEG because it provides us with a high temporal resolution and can give insights into oscillatory signatures, especially the spectral and spatial patterns thereof, that are directly linked to cellular mechanisms. A neural mass modeling approach attributed slowing of alpha in AD using MEG to neuronal hyperactivity, though without directly fitting to the empirical data [44]. Another modeling approach examined different stimulation strategies to preserve functional network integrity in AD and found that stimulating excitatory neurons were the most successful [45]. Another virtual brain simulation approach integrated local field potential simulations with regional amyloid-$\beta$ and tau uptake as empirical features to classify healthy controls,
MCI, and AD and obtained an average F1 score of 0.743 [46] – our study reports a higher F1 score of 0.77 for classification of AD from controls with just a few parameters as features of a random forest classifier.

A key difference from prior modeling approaches is that our SGM is a linear model with a small set of biophysically interpretable global parameters. Therefore, it can be obtained in a closed-form solution in the frequency domain and model parameter inference is more tractable. We employed SGM because prior studies indicate that the emergent macroscopic activity is independent of the microscopic activity of individual neurons [37–39, 47, 40, 41], and is primarily governed by the long-range connections [48–51]. Indeed, it was already demonstrated that SGM outperforms a Wilson-Cowan neural mass model in fitting the empirical MEG spectra [25]. A recent comparison showed that linear models outperformed non-linear models in predicting resting-state fMRI time series. This was attributed to the linearizing effects of macroscopic neurodynamics and neuroimaging due to spatial and temporal averaging, observation noise, and high dimensionality [52]. Given that the vast majority of computational models involving neural masses involve highly non-linear concepts like multistability, metastability, and other complex dynamics [53–57], it may be questioned whether AD-induced changes in brain macroscopic dynamics can even be reliably measured and robustly inferred. Instead, we expect that while neural activity in AD and health might be highly dynamic and non-linear, its macroscopic spatial and frequency patterns are known to be far more stable across individuals [38, 58, 59, 17, 18]. This is a key motivation for our use of the linear and deterministic SGM, which has demonstrable tractability and only a few free parameters capable of predicting spectral and regional profiles of MEG activity. To our knowledge, this is the first study identifying a parsimonious biophysically interpretable marker of AD and cognitive decline in AD.

3.5 Limitations of the current study

In this study, we aimed to capture the shape of the power spectra by using Pearson’s R as the cost function. In the future, we will aim at capturing the magnitude of the power spectra as well as selected spectral features. Further, we employed the same template structural connectome from HCP for both cohorts, in the interest of statistical tractability. With this, we can pinpoint the biophysical alterations solely due to alterations in the functional activity. In addition, a prior study has demonstrated that white matter network organization is preserved in AD [60]. In the future, however, we will obtain individual structural connectomes in AD. Lastly, we observed that the SGM fits better to spectral and spatial patterns from AD rather than from controls. This may be attributed to the spectral shape of AD – it has a clearer exponential fall-off that is easier to fit to. In comparison, the spectral shape of controls has an additional peak in the beta band superimposed on the exponential fall-off.

Notwithstanding, this work shows that a global impairment in the excitatory long-range pyramidal neuronal population is the most important indicator of AD, and is also associated with global cognitive decline in patients with AD. Our modeling approach outlines a parsimonious framework for identifying cellular correlates of abnormal electrophysiological oscillations and cognitive deficits in AD, that can aid in guiding future clinical trials.

4 Methods

4.1 Data description

88 patients with AD (diagnostic criteria for probable AD or mild cognitive impairment due to AD) [61–63] and 88 age-matched controls were included in this study. Each participant underwent a complete clinical history, physical examination, neuropsychological evaluation, brain magnetic resonance imaging (MRI), and
a 5-10-minute session of resting MEG. All participants with AD were recruited from research cohorts at the University of California San Francisco-Alzheimer’s Disease Research Center (UCSF-ADRC). Healthy control participants were recruited at UCSF-ADRC as well as from several ongoing studies at the Biomagnetic Imaging Laboratory at UCSF. Informed consent was obtained from all participants and the study was approved by the Institutional Review Board (IRB) at UCSF (UCSF-IRB 10-02245). The mean (std) age of controls (N=88) and patients with AD (N=88) was 65.07 (9.92) and 62.73 (8.64) years, respectively. 51 (58 %) of 88 controls, and 53 (60.2 %) of patients with AD were females. The mean (std) MMSE score of patients with AD was 22.14 (5.55), while the mean Clinical Dementia Rating-Sum of Boxes (CDR) score of patients with AD was 4.90 (2.75).

4.2 Clinical assessments and MEG, and MRI acquisition and analyses

All the processing pipelines are the same as that for a previous study [18]. Patients with AD were assessed via MMSE and a standard battery of neuropsychological tests. Patients with AD were assessed via a structured caregiver interview to determine the Clinical Dementia Rating.

MEG scans were acquired on a whole-head biomagnetometer system (275 axial gradiometers; MISL, Coquitlam, British Columbia, Canada) for 5–10 min, following the same protocols described previously [17, 18]. Tomographic reconstructions of source-space data were done using a continuous 60-second data epoch, an individualized head model based on structural MRI, and a frequency optimized adaptive spatial filtering technique implemented in the Neurodynamic Utility Toolbox for MEG (NUTMEG; http://nutmeg.berkeley.edu). We derived the regional power spectra based on Desikan–Killiany atlas parcellations for the 68 cortical regions depicting neocortex and allocortex, the latter including the entorhinal cortex. Regional power spectra were derived from FFT and then converted to dB scale.

4.3 Resting state MEG data acquisition

Each subject underwent MEG recording on a whole-head biomagnetometer system consisting of 275 axial gradiometers (MISL, Coquitlam, British Columbia, Canada), for 5–10 min. Three fiducial coils including nasion, left and right preauricular points were placed to localize the position of head relative to sensor array, and later coregistered to each individual’s respective MRI to generate an individualized head shape. Data collection was optimized to minimize within-session head movements and to keep it below 0.5 cm. 5–10 min of continuous recording was collected from each subject while lying supine and awake with eyes closed (sampling rate: 600 Hz). We selected a 60-s (1 min) continuous segment with minimal artifacts (minimal excessive scatter at signal amplitude <10 pT), for each subject, for analysis. The study protocol required the participant to be interactive with the investigator and be awake at the beginning of the data collection. Spectral analysis of each MEG recording and whenever available, and the simultaneously collected scalp EEG recording were examined to confirm that the 60-s data epoch represented awake, eyes closed resting state for each participant. Artifact detection was confirmed by visual inspection of sensor data and channels with excessive noise within individual subjects were removed prior to analysis.

4.4 Source space reconstruction of MEG data and spectral power estimation

Tomographic reconstructions of the MEG data were generated using a head model based on each participant’s structural MRI. Spatiotemporal estimates of neural sources were generated using a time–frequency optimized adaptive spatial filtering technique implemented in the Neurodynamic Utility Toolbox for MEG (NUTMEG; https://nutmeg.berkeley.edu/). Tomographic volume of source locations (voxels) was computed through an
adaptive spatial filter (10-mm lead field) that weights each location relative to the signal of the MEG sensors [64, 65]. The source space reconstruction approach provided amplitude estimations at each voxel derived through the linear combination of spatial weighting matrix with the sensor data matrix [64]. A high-resolution anatomical MRI was obtained for each subject (see below) and was spatially normalized to the Montreal Neurological Institute (MNI) template brain using the SPM software (http://www.fil.ion.ucl.ac.uk/spm), with the resulting parameters being applied to each individual subject’s source space reconstruction within the NUTMEG pipeline [65].

To prepare for source localization, all MEG sensor locations were coregistered to each subject’s anatomical MRI scans. The lead field (forward model) for each subject was calculated in NUTMEG using a multiple local-spheres head model (three-orientation lead field) and an 8-mm voxel grid which generated more than 5000 dipole sources, all sources were normalized to have a norm of 1. The MEG recordings were projected into source space using a beamformer spatial filter. Source estimates tend to have a bias towards superficial currents and the estimates are more error-prone when we approach subcortical regions, therefore, only the sources belonging to the 68 cortical regions were selected for further analyses. Specifically, all dipole sources were labeled based on the Desikan–Killiany parcellations, then sources within a 10-mm radial distance to the centroid of each brain region were extracted for each region. In this study, we examined the broad-band (1–35 Hz). Power spectra were derived by applying FFT on the time-course data and then converted to the dB scale.

4.5 Magnetic resonance image acquisition and analysis

Structural brain images were acquired from all participants using a unified MRI protocol on a 3 Tesla Siemens MRI scanner at the Neuroscience Imaging Center (NIC) at UCSF. Structural MRIs were used to generate individualized head models for source space reconstruction of MEG sensor data. Structural MRI scans were also used in the clinical evaluations of patients with AD to identify the pattern of gray matter volume loss to support the diagnosis of AD.

4.6 Model

The model used here is similar to the SGM developed previously [25, 26, 66, 67], and is described in detail in the supplementary document. Briefly, it is characterized by the following model parameters at the mesoscopic level: excitatory time constant ($\tau_e$), inhibitory time constant ($\tau_i$), excitatory gain ($g_{ee}$, assumed to be 1 for parameter identifiability), inhibitory gain ($g_{ii}$), coupled population gain ($g_{ei}$); and the following model parameters at the macroscopic level: coupling constant ($\alpha$), speed ($v$), graph excitatory time constant ($\tau_G$). The model solution can be obtained in a closed form in the frequency domain as a function of angular frequency $\omega$ as:

$$X(\omega) = \sum_{k=1}^{N} \frac{u_k(\omega) u_k(\omega)^H}{3\omega + \tau_G^{-1} \lambda_k(\omega) F_G(\omega)} H_{local}(\omega) P(\omega),$$

where, $X(\omega)$ is the signal of every brain region, $u_k(\omega)$ are the eigenmodes and $\lambda_k(\omega)$ are the eigenvalues obtained by the eigen-decomposition of a complex Laplacian matrix. Equation (1) is the closed-form steady-state solution of the macroscopic signals at a specific angular frequency $\omega$. We use this modeled spectra to compare against empirical MEG spectra and subsequently estimate model parameters. In practice, only a few eigenmodes $k \in [1, K], K \ll N$ are needed to obtain sufficiently strong fits to empirical data, including especially the lowest eigenmodes [26].
4.7 Model parameter estimation

The model parameter estimation procedure is same as described previously [67]. Modeled spectra was converted into PSD by calculating the norm of the frequency response and converting it to dB scale by taking $20\log_{10}(\cdot)$ of the norm. Pearson’s $r$ between modeled PSD and the MEG PSD was used a goodness of fit metric for estimating model parameters. Pearson’s $r$ between modeled and MEG PSD was computed for all 68 brain regions. Its average $r$ across all regions is referred to as the spectral correlation. Next we calculated the spatial correlation by obtaining the regional distribution of alpha band (8-12 Hz) raw power of both model $x$ and MEG $y$. Then, the spatial correlation was defined as $x^T \|(C + wI)\| y$, where $C$ is the row degree normalized structural connectivity matrix, $I$ is the identity matrix, $w$ is an empirical weight, and $\|(C + 10I)\|$ is the row normalized version of $C + 10I$. The objective function for optimization and estimation of model parameters was the sum of spectral and spatial correlations. We used a dual annealing optimization procedure in Python for performing parameter optimization [68].

Parameter initial guesses and bounds for estimating the static spectra are specified in Table 1. We defined three different bounds on the neural gain terms to ensure that the model is stable, based on prior work on model stability [66]. First, we supplied a larger bound on the neural gains for optimization. If the optimal model parameter was outside the stability boundary, we repeated optimization with a smaller bound. We repeated this procedure 3 times to ensure that the final optimal model parameters correspond to the stable model solutions. We used a dual annealing optimization procedure in Python for parameter optimization [68]. The dual annealing optimization was performed for three different initial guesses, and the parameter set leading to maximum sum of spectral and spatial correlations was chosen for each subject. The dual annealing settings were: maxiter = 500. All the other settings were the same as default.

### Table 1: SGM parameter values, initial guesses, and bounds for parameter estimation for static spectra fitting

<table>
<thead>
<tr>
<th>Name</th>
<th>Symbol</th>
<th>Initial value 1</th>
<th>Initial value 2</th>
<th>Initial value 3</th>
<th>Lower/upper bound for optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excitatory time constant</td>
<td>$\tau_e$</td>
<td>0.015 s</td>
<td>0.025 s</td>
<td>0.006 s</td>
<td>[0.005 s, 0.03 s]</td>
</tr>
<tr>
<td>Inhibitory time constant</td>
<td>$\tau_i$</td>
<td>0.01 s</td>
<td>0.08 s</td>
<td>0.15 s</td>
<td>[0.005 s, 0.2 s]</td>
</tr>
<tr>
<td>Long-range connectivity coupling constant</td>
<td>$\alpha$</td>
<td>1</td>
<td>0.5</td>
<td>0.1</td>
<td>[0.1, 1]</td>
</tr>
<tr>
<td>Transmission speed</td>
<td>$v$</td>
<td>5 m/s</td>
<td>10 m/s</td>
<td>18 m/s</td>
<td>[5 m/s, 20 m/s]</td>
</tr>
<tr>
<td>Alternating population gain</td>
<td>$g_{ei}$</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>[0.001,0.7], [0.001,0.5], [0.001,0.4]</td>
</tr>
<tr>
<td>Inhibitory gain</td>
<td>$g_{ii}$</td>
<td>0.6</td>
<td>1.2</td>
<td>[0.001,2.0], [0.001,1.5], [0.001,1.5]</td>
<td></td>
</tr>
<tr>
<td>Graph time constant</td>
<td>$\tau_G$</td>
<td>0.006 s</td>
<td>0.015 s</td>
<td>0.025 s</td>
<td>[0.005 s, 0.03 s]</td>
</tr>
<tr>
<td>Excitatory gain</td>
<td>$g_{ee}$</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

4.8 Statistical analyses

Statistical tests were performed using SAS software (SAS9.4; SAS Institute, Cary, NC) and the statsmodels package in Python. To compare the neuronal parameters between the controls and patients, we used a linear mixed-effects model (PROC MIXED), to compare model parameters ($\tau_G$, $\tau_e$, $\tau_i$, $g_{ii}$, $g_{ei}$, $\alpha$, $v$), including age as a covariate into the models. We reported the estimated least-squares means and the statistical differences of least-squares means based on unpaired t-tests. We also developed univariate linear regression models to examine the associations between model parameters and MMSE and CDR scores in AD. In these models, the dependent variables included MMSE and CDR (in separate models), and the predictor variables included the model parameters we found significant between AD and controls ($\tau_G$, $\tau_e$, and $g_{ii}$). Next, we developed
multivariate linear regression models with dependent variables as MMSE and CDR (separately), and the predictor variables included all the significant parameters $\tau_G$, $\tau_e$, $g_{ji}$, and age as covariates.

4.9 Classification between AD and controls

We trained a random forest for classifying AD and controls. Here, we used the SGM parameters and age as features of the model. For training and testing, we employed a 5-fold stratified cross validation method. We divided the dataset into 5 folds and used the 4 folds for training, and the 5th fold for testing the model. We repeated this procedure 100 times. While training the model, no information of the testing fold was provided. With the 4 folds of the training dataset, further 5-fold cross validation was performed to estimate the tuning parameter of the random forest. Here, we only tuned for the max depth with the following options for max depth: None, 2, 3, 4. All other hyperparameters were kept as default in the sklearn package in Python. After estimating the tuning parameter, the model was trained using the entire training dataset and then tested on the 5th fold. The mean AUROC of the test dataset was finally reported. The feature importance was estimated as the average of the feature importance from the random forest classifier that was trained 100 times.

Acknowledgments

This work was supported by NIH grants R01NS092802, R01NS183412, R01AG062196, R01AG072753, R01EB022717, R01DC013979, R01NS100440, R01DC176960, R01DC017091, UCOP-MRP-17-454755, Alzheimer’s Association grant AARFD-22-923931, and an industry research contract from Ricoh MEG Inc. The template Human Connectome Project (HCP) connectome used in the preparation of this work was obtained from the MGH-USC HCP database (https://ida.loni.usc.edu/login.jsp). The HCP project’s MGH-USC Consortium (Principal Investigators: Bruce R. Rosen, Arthur W. Toga and Van Wedeen; U01MH093765) is supported by the NIH Blueprint Initiative for Neuroscience Research Grant; the National Institutes of Health grant P41EB015896; and the Instrumentation Grants S10RR023043, 1S10RR023401, 1S10RR019307. Collectively, the HCP is the result of efforts of co-investigators from the University of Southern California, Martinos Center at Massachusetts General Hospital (MGH), Washington University, and the University of Minnesota.

Data availability

The code for this work is available here: https://github.com/parulv1/sgm-ad. Anonymized subject data will be shared on request from qualified investigators for the purposes of replicating procedures and results, and for other non-commercial research purposes within the limits of participants’ consent. Correspondence and material requests should be addressed to Kamalini.ranasinghe@ucsf.edu.

References


Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SGMADsupplementary.pdf