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Article

Predictions of neural control deficits in elders with subjective memory complaints and Alzheimer's disease

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SUMMARY

Alzheimer's disease (AD) is a common disease, affecting over 6 million elders in the U.S in 2024. However, AD remains untreatable due to the absence of an effective biomarker to assess the underlying deficits in cognitive control. Disruptions in the brain's control systems are key factors in the learning and memory impairments that define AD. In this study, we hypothesized that we could predict neural control deficits in elders with subjective memory complaints (SMC) and AD patients using Diffusion Tensor Imaging (DTI) data and brain controllability analysis. DTI is a non-invasive neuroimaging tool that detects how fluid travels along the white matter tracts inside the brain. To test our hypothesis, we used the DTI data of 12 elders with SMC, 12 AD patients, and 12 healthy subjects from the open-source dataset Alzheimer's Disease Neuroimaging Initiative. First, we constructed individual brain connectivity networks. Using graph theory and brain controllability analysis, we assessed node degree and controllability. We then averaged these measures across brain areas to calculate global metrics for each subject. Results illustrated that the node degree could not identify SMC and AD from healthy subjects, while the controllability measure could differentiate SMC and AD from healthy subjects and distinguish between SMC and AD. In conclusion, this study provides a promising biomarker for detecting neural control deficits in elders with SMC and AD patients for future clinical application.

INTRODUCTION

Alzheimer's disease (AD) is a prevalent and progressive neurodegenerative condition marked by memory loss, cognitive impairments, and changes in behavior (1). It stands as one of the primary causes of illness and death among the elderly, impacting over 6 million people in the United States as of 2024 (2). Despite extensive research and many clinical trials, AD continues to be incurable (3). A major obstacle in creating effective treatments and prevention strategies for AD is the lack of dependable biomarkers to evaluate the neural control deficits that are fundamental to the cognitive difficulties associated with the disease (4). A better understanding of these neural control deficits could provide an avenue for early diagnosis and targeted treatment strategies, thereby improving clinical outcomes. Conventional neuroimaging techniques, including magnetic resonance imaging (MRI) and positron emission tomography (PET) scans, offer limited insights into the microstructural properties of brain networks that may hold the key to understanding neural control deficits (5). Thus, there is an urgent need for new methodologies that can provide a more comprehensive map of brain dysfunction in AD without causing harm to patients.

Diffusion tensor imaging (DTI) is a non-invasive neuroimaging technique that shows promise as an alternative tool for the detection of AD (6). DTI measures the diffusion of water molecules along the white matter tracts, providing insights into the structural connectivity of the brain (7). This modality has the potential to capture subtle variations in the microstructure of brain networks that may be indicative of neural control deficits related to AD. The neural system is a complex network facilitating point-to-point connections for rapid coordination. In AD patients, this intricately structured network becomes disrupted, resulting in impaired neural control. This disruption is a critical factor contributing to the deficits in learning and memory observed in AD (8). Building upon the abilities of DTI, brain controllability analysis offers a sophisticated tool for understanding the complex interplay between different brain regions (9). Network controllability is a recent concept in network neuroscience that aims to forecast how individual cortical sites influence overall network states and their transitions, offering a cohesive framework for understanding local effects on global brain dynamics (10). This approach, grounded in control theory, offers a dynamic interpretation of brain states, contrasting with conventional static network metrics like efficiency, degree, and strength (11). By analyzing the network architecture of the brain, one can evaluate how efficiently information is propagated and processed, thereby providing potential indicators of neural control deficits. While traditional graph-based metrics reveal the local properties and significant roles of various brain areas within their network architectures, control theory-based network measures uniquely quantify the capability of a single brain region to induce changes in overall brain behavior, transitioning from one state to another (9).

Brain controllability, a concept derived from control theory, offers a groundbreaking tool for understanding neural dynamics (9). Unlike traditional graph theory, which provides a descriptive measure of network structures, brain controllability furnishes predictive insights into how these neural networks might evolve over time. This becomes profoundly important when investigating cognitive control impairments in AD. Within the brain, controllability metrics measure the ability of individual regions to initiate changes that affect broader neural circuits, steering them from any initial state to a specific, desired state within a finite time. This application of brain controllability to the study of AD provides crucial framework for assessing the cognitive control impairment. Understanding brain controllability could offer invaluable

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insights into the neural deficits that contribute to cognitive control impairment in AD, thereby opening new avenues for diagnosis and targeted interventions and treatments.

The objective of the present study was to explore the potential of utilizing DTI data along with brain controllability analysis to predict neural control deficits in elders with subjective memory complaints (SMC) and patients with AD. Individuals with SMC experience cognitive symptoms or concerns without demonstrable alterations in objective psychometric assessments (12). SMC describes self-reported memory issues not evident in standard cognitive tests with no clinical signs of significant memory loss, while AD diagnosis combines clinical assessment, imaging, and biomarkers (13). While SMC may be an early sign of AD, progression to AD is not certain and often precedes mild cognitive impairment (MCI), a detectable decline not as severe as dementia (13). SMC increases the risk of developing MCI and possibly AD but not for everyone (13). The inclusion of SMCs in this study aimed to explore neural control patterns that may be indicative of an early stage of AD, which could be pivotal for prompt diagnosis and intervention.

For this study, we employed an open-source dataset from the Alzheimer's Disease Neuroimaging Initiative (ADNI), comprising DTI data from 12 elders with SMC (F/M: 7/5, age: 72.3 ± 3.7), 12 patients with AD (F/M: 6/6, age: 74.3 ± 8.5), and 12 healthy controls (HC) (F/M: 7/5, age: 72.1 ± 6.4) (14). We hypothesized that brain controllability measures could differentiate between healthy subjects, those with SMC, and patients with AD, thereby providing a promising biomarker for clinical applications. The need for a reliable, non-invasive biomarker to diagnose and monitor Alzheimer's disease is pressing. Our findings indicated that node degree measurements were insufficient to differentiate SMC and AD from healthy individuals. However, the brain controllability metrics were significantly more effective in identifying neural control deficits, distinguishing SMC and AD from healthy subjects and from each other. In conclusion, brain controllability measures showed promise as biomarkers for the detection of neural control deficits in elderly individuals with SMC and AD, with potential for future clinical applications.

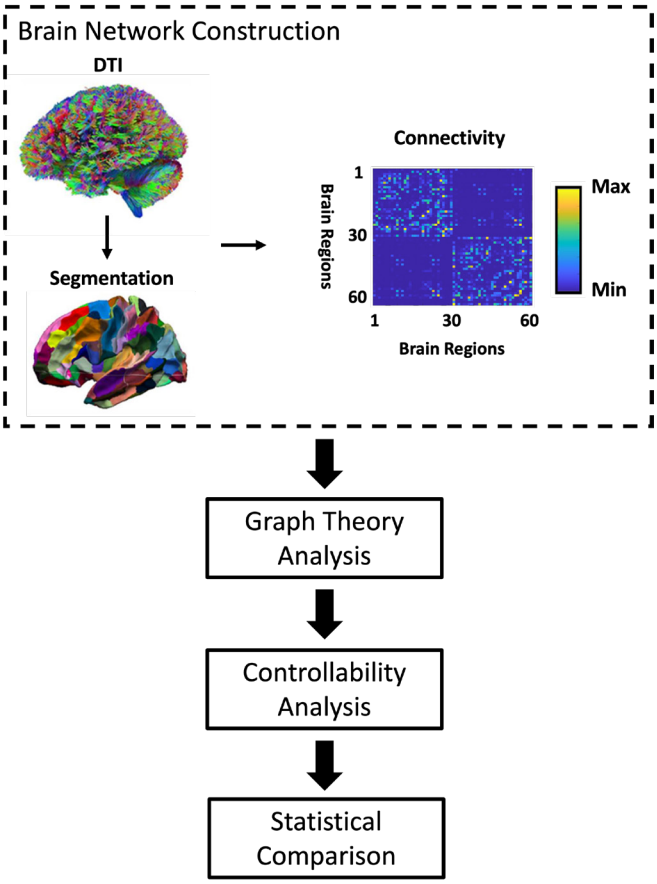

Figure 1: Data Pre-Processing and Post-Processing Procedures. We first processed the DTI data to calculate the number of streamlines connecting each two brain areas and constructed the brain connectivity network. We employed graph theory to compute the node degrees and applied the brain controllability analysis to calculate the controllability of each single brain area. Furthermore, we averaged the node degree and controllability measures across all brain areas, respectively, to compute the global node degree and global controllability of each single subject and performed statistical analysis to compare the node degree and brain controllability between various groups.

RESULTS

Brain Connectivity Network of HC, SMC, and AD

The overall data processing procedures consisted of brain network construction, graph theory analysis, controllability analysis and statistical comparison (**Figure 1**). We first plotted the averaged structural brain connectivity network in each group to visualize the connectivity distribution in each group (**Figure 2**). From the results, we could not visualize the difference between groups. We then calculated the global node degree, defined by the average of all connections across various brain areas, for each individual. We further employed the student t-test to compare the global node degree between different groups of subjects, including HC, SMC, and AD . The graphical measurement of node degree could not differentiate between HC, SMC, and AD ($P > 0.05$) (**Figure 3**).

Global Brain Controllability of HC, SMC, and AD

We then calculated the brain controllability of each subject's brain area based on the constructed brain connectivity network and averaged across brain regions in each subject. Student t-test was then utilized to compare the global controllability between HC, SMC, and AD subjects. FDR correction was further applied to correct the *p*-value after multiple comparisons. From the results, we can see that the there is a significantly decreased trend from HC to SMC ($P = 0.0175$), HC to AD ($P = 0.0001$), and SMC to AD ($P = 0.0303$) (**Figure 4**).

DISCUSSION

This study set out to explore the potential utility of DTI combined with brain controllability analysis in assessing neural control deficits in AD and SMC. Our findings demonstrated that brain controllability measures could be more effective than traditional node degree measures for distinguishing between healthy elders, those with SMC, and patients with AD. The results not only verified our hypothesis but also open new avenues in the identification of a non-invasive biomarker for cognitive control deficits related to AD and SMC.

AD is a debilitating condition that affects over 6 million elderly individuals in the U.S. as of 2024. The absence of reliable biomarkers for early detection remains a significant

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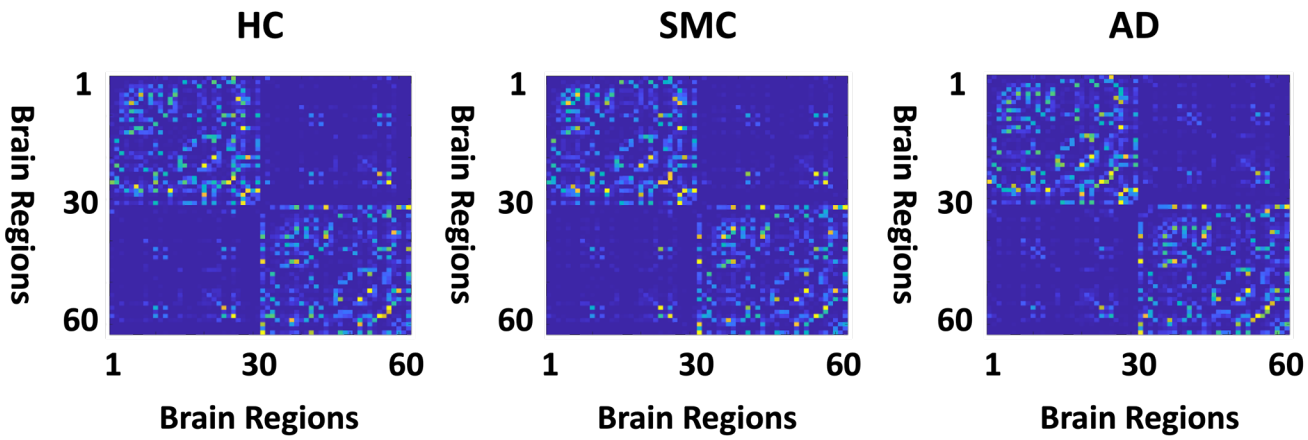

Figure 2: Brain Connectivity Network of healthy controls (HC), individuals with subjective memory complaint (SMC), and patients with Alzheimer's disease (AD). Each element within the matrix represents the number of streamlines connecting each two brain areas.

barrier to effective diagnosis and treatment. Therefore, the findings of this study are important, as they could offer an avenue for early detection of cognitive decline to choose alternative intervention and targeted therapies, potentially altering the trajectory of these degenerative conditions.

Our findings draw strength from previous research that also emphasized the utility of brain network control theory in understanding various neural and cognitive processes (9). The concept of 'controllability' in the structural brain networks adds theoretical robustness to our study (9). In the context of AD, a prior study identified altered white matter integrity using DTI, which aligns with our method and results (**Figure 4**) (15). Our findings also showed that the overall control capabilities of the brain in AD patients were compromised, potentially making it difficult for them to regulate their cognitive state. This study not only supports our choice of DTI as a valid imaging technique but also underscores the important role of brain controllability as a potential biomarker for evaluating the neural control deficits as it can be used to identify AD from HC and SMC. When this controlling capability is compromised in AD, the ability for task-specific modulations and the adaptive tuning of neural dynamics may be impaired, contributing to observable cognitive decline. Further, previous evidence identified structural network alterations in AD and SMC, supporting our focus on these conditions for identifying AD and SMC (16).

The ability to accurately diagnose AD and SMC at an early stage would represent a key step in neurology and geriatric medicine. Our results could help provide clinicians with a non-invasive, reliable biomarker that can be used for early detection and monitoring of AD and SMC. This would not only enable more timely interventions but also offer patients and their families an opportunity to make informed decisions about care and treatment options. The clinical translation of our findings could thereby lead to more personalized medicine approaches and ultimately improve patient outcomes.

While our study offers important contributions, it is essential to consider its limitations. The generalizability of our findings may be constrained by our small sample size of 12 subjects per group, all drawn from the ADNI database. To substantiate the conclusions of this study, future research should involve a more extensive sample pool. The current study is confined to the use of DTI for identifying structural brain alterations, excluding functional dynamics. Future research will incorporate functional neuroimaging techniques, such as functional MRI (fMRI), to discern functional brain changes in patients with SMC and AD in contrast to healthy individuals.

Prior research has also suggested that the effectiveness of DTI measures, network diagnostics, and controllability parameters could be influenced by different acquisition parameters and pre-processing steps, which will further be investigated and discussed in future studies (17). A notable limitation of this study pertains to the selection criteria of AD patients. The stages of AD progression were not accounted for, potentially affecting the identification of early-stage AD. To address this, future research will aim to narrow the patient selection to those in the preliminary stages of the disease, thereby mitigating this issue. Additionally, the present study is of an observational nature, which means we can only discern the significant differences between the healthy controls, the SMC group, and the AD group. However, we have not employed any classifier to verify the accuracy of such distinctions. In future research, we plan to utilize various

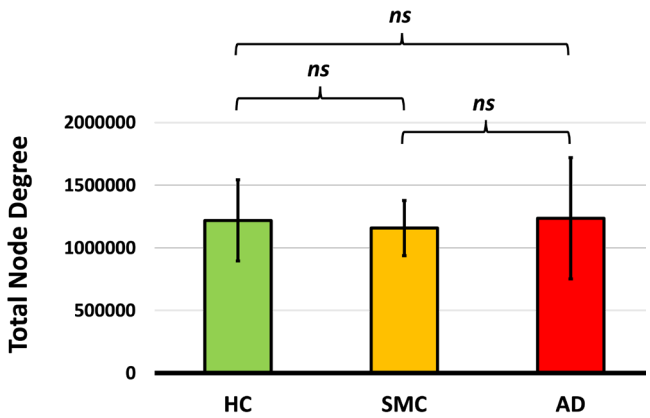

Figure 3: Total node degree comparison between HC, SMC, and AD. Student t-test was used to compare the total (global) node degree between different groups. The error bars represent standard deviation. The "ns" represents not significant.

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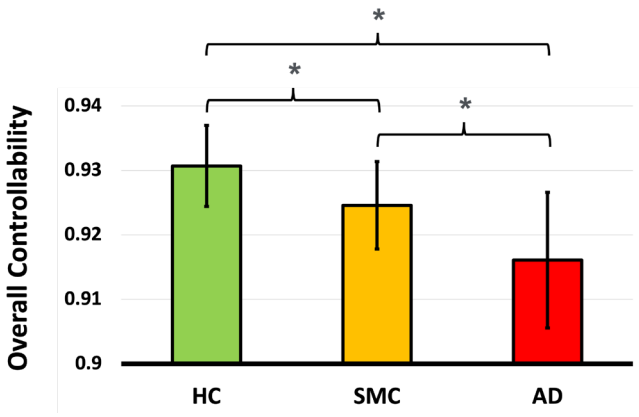

Figure 4: Overall controllability comparison between HC, SMC, and AD. Student t-test was used to compare the overall (global) brain controllability between different groups. The error bars represent standard deviation. *p < 0.05.

machine learning algorithms to categorize these distinct groups.

In conclusion, this study verifies the feasibility of using brain controllability metrics as potential biomarkers in identifying neural control deficits linked to AD and SMC. Despite limitations, the study validates the potential of our findings in early detection of AD for future clinical application. Therefore, this research lays a foundation for subsequent studies aimed at fine-tuning and further validating these initial results.

MATERIALS AND METHODS

Preprocessing of DTI Data

DTI data were pre-processed and reconstructed utilizing the DSI Studio software package (available at http://dsi-studio.labsolver.org/). We first utilized the q-space diffeomorphic reconstruction (QSDR) technique to reconstruct the DTI data. The QSDR algorithm (18) is a model-less reconstruction approach that applies spatial normalization to diffusion data. QSDR transforms the distribution of diffusion spins to a template space based on a given deformation field, and the transformed distribution can be used to calculate the spin distribution function, which quantifies the number of spins that diffuses at any orientation. We then calculated the quantitative anisotropy (QA) values and warp scans to a template QA volume in MNI space via SPM nonlinear registration. Data acquisition included 41 diffusion sampling directions and a b-value of 1000 s/mm². In-plane resolution was 1.3672 mm and slice thickness was 2.7 mm. We verified b-table orientation through a comparative analysis and used a diffusion sampling length ratio of 1.25. For fiber tracking, a deterministic algorithm with augmented strategies was used. The angular threshold varied from 15 to 90 degrees, and the step size ranged from 0.5 to 1.5 voxels. Tracks between 30 mm and 200 mm were analyzed. We then generated 1 million tracts and used the parcellation scheme of FreeSurferDKT_Cortical atlas for brain segmentation and network construction (19). This study utilized the FreeSurfer Desikan-Killiany-Tourville Cortical atlas to delineate the brain into distinct regions of interest based on gyral morphology, encompassing 35 cortical areas (19). We then constructed the brain connectivity network by quantifying the number of fiber tracts connecting each pair of brain regions from the DTI data. Connectivity matrices were created by counting track connections between regions, followed by graph theoretical analysis for node degree calculation (20). All analyses mentioned above were done in the DSI Studio toolbox.

Brain Controllability Analysis

A crucial step in applying network control theory to the human brain involves establishing a model for the dynamics of neural processes. In this study, we used a simplified, noise-free, linear, and time-invariant model to construct the dynamic model of the brain network (9). The model equation can be formulated as follows:

$$x(t+1) = Ax(t) + Bu(t) \qquad \text{(equation 1)}$$

where x describes the state of brain regions over time, and A is the structural connectivity matrix constructed by the fiber tracking method on DTI data. The input matrix B specifies the control nodes and the input u denotes the external stimulation.

Controllability was then used to assess the ability of various brain regions to steer the network system into states of varying ease (9). It was calculated as the H_2-norm of the network system. Mathematically, it was defined as:

$$a_c = Trace\left(\sum_{\tau=0}^{\infty} A^{\tau} B_k B_k^T A^{\tau}\right) \qquad \text{(equation 2)}$$

From a cognitive perspective, brain areas with high controllability are crucial because they enable the brain to transition efficiently between different cognitive states that require minimal cognitive effort (9).

Statistical Analysis

The node degree and brain controllability were averaged across the brain regions to obtain the global node degree and brain controllability for each subject. The student's t-test was then utilized to statistically compare the global node degree and global controllability, respectively, between HC, SMC, and AD groups. An alpha of 0.05 was defined as a statistically significant difference. False discovery rate method was used to correct the p-value after multiple comparisons.

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