COMPENSATORY BRAIN CONNECTION DISCOVERY IN ALZHEIMER'S DISEASE

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ABSTRACT

Identification of the specific brain networks that are vulnerable or resilient in neurodegenerative diseases can help to better understand the disease effects and derive new connectomic imaging biomarkers. In this work, we use brain connectivity to find pairs of structural connections that are negatively correlated with each other across Alzheimer's disease (AD) and healthy populations. Such anti-correlated brain connections can be informative for identification of compensatory neuronal pathways and the mechanism of brain networks' resilience to AD. We find significantly anti-correlated connections in a public diffusion-MRI database, and then validate the results on other databases.

***Index Terms*—**Alzheimer's disease, brain connectivity, diffusion MRI, compensatory pathways, anti-correlation.

1. INTRODUCTION

Debilitating neurodegenerative diseases such as Alzheimer's disease (AD) affect not only individual brain regions, but also connectivity between them [1]. The complex structural and functional brain networks through which information flows – i.e., the human *connectome* – can be mapped by means of noninvasive diffusion-weighted magnetic resonance imaging (dMRI) and resting-state functional MRI (rs-fMRI), respectively. Such a map can help to better understand the vulnerability and resilience of these networks to disease effects, potentially leading to the discovery of diagnostically and therapeutically important imaging biomarkers.

Connectivity attenuation in AD patients is often accompanied by brain reorganization and plasticity [2, 3]. Early in the disease, connectivity within some (e.g., frontal) brain regions increases – possibly due to a compensatory reallocation of cognitive resources – but eventually declines as the disease progresses [4-6]. This transient resiliency of the brain networks has been argued to help preserve some memory and attention ability in early AD [7]. In fact, the variability in performance of AD patients with the same pathological burdens [8] may be due to the high level of performance maintained [9] through adaptive recruitment of atypical brain pathways. Amplified by factors such as more years of education [10], compensatory mechanisms in the connectome have been speculated to mitigate cognitive decline and therefore contribute to *cognitive reserve* [7].

At the level of the synapses [11], a transient rise in presynaptic proteins and markers [12] and in synaptic size (to preserve synaptic density) [13] during neurodegeneration marks the brain's reorganization at early stages of AD, which is, however, disrupted at the later stages compared to healthy aging [14]. Regional compensatory synaptic mechanisms might correspond to higher brain activity [15]. Examples are: increased frontal activation in AD [16, 17]; increased hippocampal activation in elderly cognitively normal (CN) subjects with tau tangle accumulation [18] or cortical thinning [19] and in mild cognitive impairment (MCI) patients with positive amyloid beta (Aβ) plaques [20]; and increased functional connectivity within the medial temporal lobe in MCI [21-23], within the default mode network (DMN) in healthy APOE carriers [24], and in the medial prefrontal cortex in Aβ-positive elderly CN subjects [25]. Furthermore, structural enhancements such as higher diffusion fractional anisotropy (FA) [26-28] and increased cortical thickness and caudal volume [29] in populations at risk of AD and MCI subjects have been observed.

Reorganization of the brain networks in AD not only can serve as a potential early AD biomarker, but provides hope for rehabilitation [30]. Compensatory enhancement in connectivity is important to identify, since on the one hand it is useful for differential diagnosis, such as distinguishing behavioral variant frontotemporal dementia (bvFTD) from AD [31], and on the other hand it can complicate the relationship between brain pathology and functional measures when present along with degeneration in prodromal AD [11]. Moreover, the high metabolic activity resulting from the compensatory strategy of hyperactivation may eventually be deleterious for cognitive performance and accelerate pathology [32, 33].

While local brain connectivity decreases in AD, global connectivity has been seen to remain initially stable [34]. This suggests that affected cognitive processes may be relying on alternative brain networks for compensation, facilitated by the brain's plasticity [35]. Although hyper-connectivity in a network is often accompanied by connectivity disruption within a reciprocal network, most existing studies monitor

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compensatory effects in a network with respect to the progression of dementia, but few do with respect to the deterioration of other networks. As an example of the latter, AD patients have been shown to rely on increased frontal connectivity to compensate for reduced temporal connectivity [36, 37]. Moreover, AD has been shown to reduce connectivity in DMN but intensify it at the early stages in the *salience network* – a collection of regions active in response to emotionally significant stimuli – whereas bvFTD has been shown to attenuate the salience network connectivity but enhance the DMN connectivity [5, 31]. Inverse relationship has been observed between the connectivity strengths of these two neural systems across dementia populations (in addition to their rs-fMRI signal anti-correlation) [31]. Nonetheless, we are not aware of an exploratory study to discover pairs of anti-correlated brain connections, in each of which one connection is significantly stronger across the population only if the other is weaker.

In this work, we attempt to identify potentially compensatory enhancement of structural connectivity in AD via the negative (cross-subject) interrelationships among brain connections. As opposed to focusing only on the relationship between connectivity and the clinical data, we identify *pairs* of connections that are significantly negatively correlated with each other, and evaluate replicability on external datasets. Our underlying hypothesis is that such a connection-wise correlation approach can help to reveal pathways that are potentially compensatory and define the resilience mechanism of brain networks against AD. To that end, we apply our previously validated conductance-based model of structural connectivity [38, 39] – that accounts for multi-synaptic connections – to three public dMRI databases:

- the second phase of the *Alzheimer's Disease Neuroimaging Initiative (ADNI-2)* [40],
- the third release in the *Open Access Series of Imaging Studies (OASIS-3)* [41], and
- the WashU-UMN *Human Connectome Project (HCP)* [42].

In the following, we describe the proposed method in detail (Section 2), present (Section 3) and discuss (Section 4) experimental results, and conclude the paper (Section 5).

2. METHODS

2.1. Data Processing

We apply our conductance-based connectivity computation method [38] (www.nitrc.org/projects/conductance) on dMRI data to compute the connectivity among $N = 86$ FreeSurfer-segmented [43] subcortical and cortical regions of interest (ROIs) from 213 CN, MCI and AD subjects of *ADNI-2*, 270 CN, MCI and AD subjects from *OASIS-3* (its largest subset of subjects sharing identical scan description), and 100 young adult subjects from *HCP*, resulting in a symmetric $N \times N$ connectivity matrix for each subject. We also include functional correlation matrices from HCP, which have previously been generated [38, 42] from four stacked sessions of rs-fMRI.

2.2. Identification of Anti-Correlated Connections

We first vectorize the lower triangular part of each matrix to a vector of length $N(N-1)/2$, and reduce this vector to keep M cortico-cortical and cortico-subcortical connections. We then compute the cross-subject linear correlation coefficient between each pair of connections, resulting in two symmetric $M \times M$ connection-wise matrices of correlations, R, and p-values, P. We then keep only the connection pairs with a correlation value smaller than a negative threshold, e.g. -0.1, as $\mathcal{R}^- \coloneqq \{(i,j) | R_{i,j} < -0.1\}$. From that set, we consider the pairs whose p-values survive a cutoff threshold, namely $\alpha = 0.05$, as $\mathcal{S} \coloneqq \{(i,j) \in \mathcal{R}^- \,|\, P^*_{i,j} < \alpha\}$. P^* is the set of p-values corrected for multiple comparisons among the elements of $\mathcal{R}^-$ with the Holm-Bonferroni method. We regard the surviving set $\mathcal{S}$ as the pairs of connections with significant cross-subject anti-correlation. We keep either the entire $\mathcal{S}$, or reduce it to a most significant subset of it.

Next, to *externally* test if the surviving set $\mathcal{S}$ is anti-correlated, we compute R_{test} and P_{test} for the connection pairs in $\mathcal{S}$ in a different population, and verify both $R_{\text{test}} < 0$ and $P^*_{\text{test}} < \alpha$ for that set, with P^*_{test} being P_{test} corrected for multiple comparisons among the pairs in $\mathcal{S}$. We will also test the hypothesis that the surviving pairs of connections are left-right symmetric; i.e., whether a significant anti-correlation is also a significant anti-correlation in the mirrored hemisphere.

Lastly, we correlate the identified connections with cognitive performance measures, such as the Clinical Dementia Rating (CDR) and the Mini-Mental State Examination (MMSE) score.

3. EXPERIMENTAL RESULTS

3.1. Anti-Correlated Connections

For ADNI-2, we computed the cross-subject linear correlation coefficient between all pairs of structural connections, keeping $|\mathcal{R}^-| = 1978$ pairs for which $r \coloneqq R_{i,j} < -0.1$. From those, the correlation between the left cortico-subcortical insula-caudate connection and the left cortico-cortical precentral-entorhinal connection (Figure 1, top, left) was most significant ($p = 3\times10^{-6}$, $p_{\text{Bonferroni}} = 0.006$) with r = -0.31 and the robust (bisquare) fit slope m = -0.40. (The top 20 significant pairs in $\mathcal{S}$ all involved the insula-caudate connection.) The correlation coefficients (r) and the p-values were computed using the `corr` function of Matlab.

We then tested whether the same two connections were inversely correlated also in the right hemisphere, which was true with high significance (r = -0.15, p = 0.03, m = -0.24; Figure 1, top, right). Since here we tested a specific pair of connections in the right hemisphere, correction for multiple comparisons was not needed.

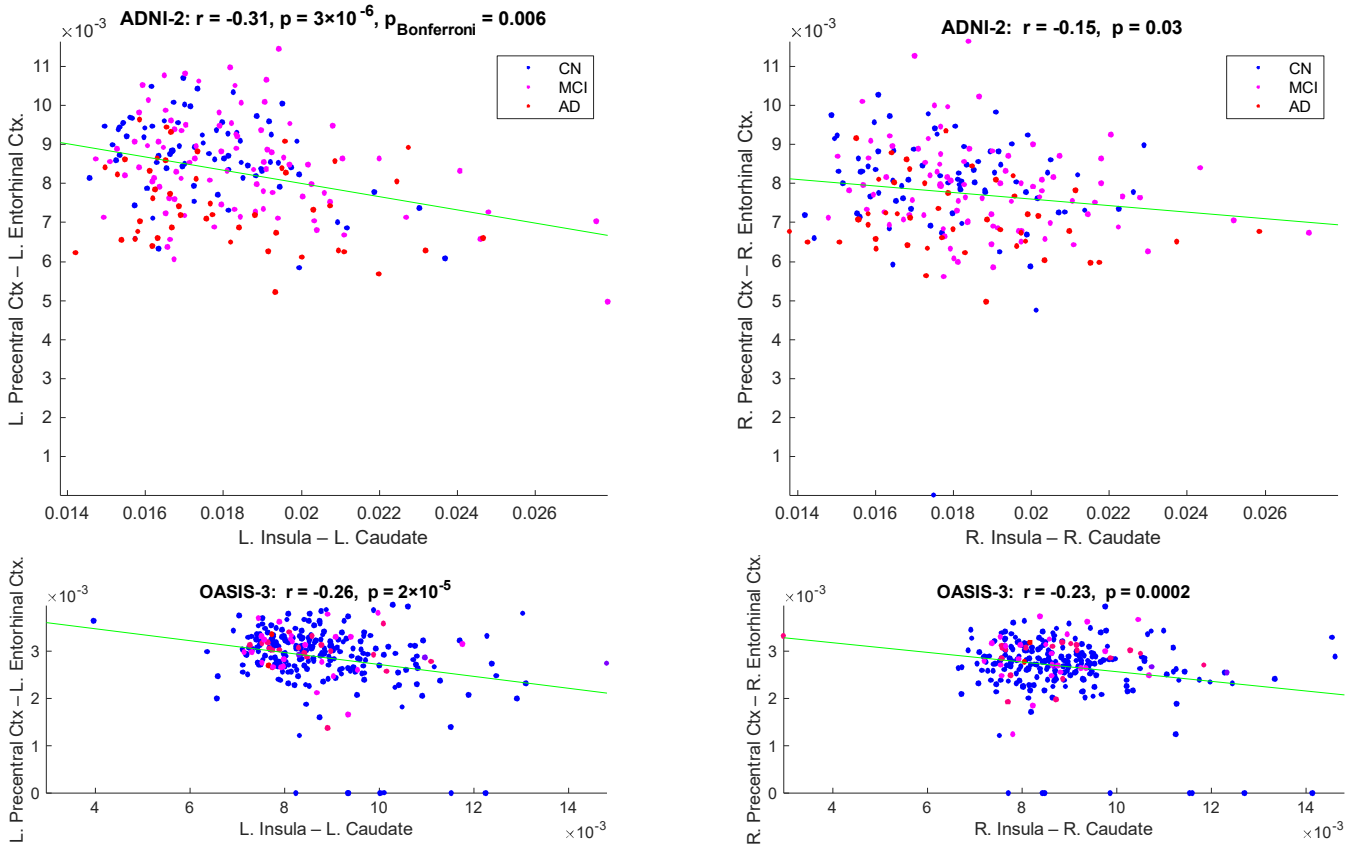

Figure 1. Negative correlation between the insula-caudate and the precentral-entorhinal structural connections in the *left* and *right* hemispheres, across the ADNI-2 (*top*) and OASIS-3 (*bottom*) populations.

Next, for external validation and replication, we tested the hypothesis that the pair of insula-caudate and precentral-entorhinal connections are negatively correlated, this time in the OASIS-3 database. This hypothesis was validated with this new dataset in both the left ($r = -0.26$, $p = 2\times10^{-5}$, $m = -0.48$) and the right ($r = -0.23$, $p = 0.0002$, $m = -0.28$) hemispheres (Figure 1, bottom).

We then computed the correlation with the CDR and the MMSE score in the OASIS-3 database. While the CDR was negatively correlated with mean connectivity ($r = -0.22$, $p = 0.0002$), it was positively correlated with the caudate-insula connection in the left ($r = 0.19$, $p = 0.001$) and right ($r = 0.22$, $p = 0.0002$) hemispheres. Likewise, whereas the MMSE score was positively correlated with mean connectivity ($r = 0.19$, $p = 0.001$), it was negatively correlated with the caudate-insula connection in the left ($r = -0.12$, $p = 0.046$) and right ($r = -0.12$, $p = 0.041$) hemispheres.

3.2. Null Results

In contrast, we did not observe any negative correlation between the insula-caudate and precentral-entorhinal connections across the young-adult HCP subjects, either in structural or functional connectivity.

By reversing the order of ADNI-2 and OASIS-3 databases in this experiment, the most significantly anti-correlated pair found in OASIS-3 was not negatively correlated in ADNI-2. In addition, the anti-correlation between the insula-caudate and precentral-entorhinal connections was not observed in OASIS-3 when we included most (740) OASIS-3 subjects, which had heterogeneous scan descriptions (as opposed to our subset of 270 subjects with identical scan descriptions).

4. DISCUSSION

Increased FA in the left caudate, which could cause the connectivity quantification algorithm to output an elevated caudal structural connectivity, has been reported in pre-symptomatic familial AD subjects [26]. This is consistent with our findings, especially given the more significant anti-correlation in the left hemisphere. Increases in structural connectivity in the right insula [44] and in functional connectivity between the frontal lobe and the corpus striatum [36] in AD have also been reported. Our conductance method [38] quantifies structural connectivity between a pair of regions as the total connectivity through all paths between the pair. Caudate-insula connectivity thus includes indirect paths passing through, e.g., thalamus or putamen, both of which

have been shown to have enhanced structural connectivity in AD [26, 44]. Furthermore, the fact that such a negative correlation was observed consistently in older adults and those on the dementia spectrum (ADNI-2 and OASIS-3), but not in young healthy adults (HCP), suggests that this significant anti-correlation might be due to progression of dementia and/or aging, and possibly a compensatory effect.

Including all OASIS-3 subjects (as opposed to only the subset with homogeneous scans) did not externally validate the hypothesis generated from ADNI-2, possibly because the various acquisition parameters created a large variance in the data that dominated the putative compensatory effects.

It is important to note that an increase in the measured structural connectivity could stem from factors other than an actual strengthening of the tract. White-matter atrophy, volume reduction [45], and other geometrical variabilities could make ROIs closer to each other, leading to elevated measured structural connectivity. Additionally, in regions with fiber crossing, selective axonal loss can lead to an increase in FA and subsequently overestimation of structural connectivity [26-28]. Similarly, functional connectivity enhancement in preclinical AD might be attributed to factors other than compensation; for instance, excitotoxicity related to Aβ pathology early in AD [25, 46] and disruptions in reciprocal inhibition in anti-correlated networks [17, 47, 48] can possibly explain aberrant hyper-connectivity.

Future work will consist of studying the relationship between the identified connections and cognitive performance on *longitudinal* data to elucidate whether compensation is at work. For instance, if intensified salience network connectivity in early AD is associated with preserved episodic memory, it may imply that this network enhancement provides compensation [47]; otherwise, it may indicate a disinhibition [49] and consequently over-sensitization of the network (especially if accompanied with anxiety and agitation) [31].

5. CONCLUSIONS

We have correlated brain connections with each other across Alzheimer's disease and healthy populations and discovered significantly anti-correlated structural connections. Future work consists of using longitudinal data to further test the hypothesis that such connections are indeed compensatory.

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