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Short Communication

# Link Clustering to Explore Brain Dynamics Using Resting State Functional MRI

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**Abstract**

Quantitative network analysis of brain networks has been an important tool for characterizing brain function. Cognitive abilities emerge from coordinated activity of distributed brain regions that may participate in multiple networks at different times. However, neuroimaging has few available tools to model and quantify networks with spatially overlapping nodes that are active at different times. The dynamics of network reconfiguration may yield important insight into networks that are damaged with neurodegenerative disease. We describe here an approach that uses a graph analytic technique called link clustering, which identifies communities that have overlapping functional nodes, demonstrating its ability to highlight differences in the dynamic reorganization of networks between subjects with Alzheimer's dementia and normal controls.

## INTRODUCTION

Higher cognitive abilities (e.g., memory, executive function) emerge from coordinated activity of distributed cortical regions, each relatively specialized for one or more aspects of the function. The composition of such systems is enabled by patterns of anatomical connectivity, but shifts dynamically. A single cortical field may be involved in multiple distributed systems [1-3]. Thus, a functional magnetic resonance imaging (fMRI) scan of a subject at rest (resting fMRI), normally 6-10 minutes in length, may allow us to study the dynamics of these cortical systems. Convergent evidence supports the hypothesis that strength of correlation between brain regions (aka functional connectivity) is related to efficiency of communication: patterns of correlations recreate spatial maps of known large-scale intrinsic brain networks [4], and a disruption of "normal" patterns of mean correlations obtained during resting state scans (mean connectivity) has been related to aging [5,6] Alzheimer's [7-9], and a variety of neuropsychiatric disorders. Functional connectivity provides unique information about systems-level brain function not obtainable through structural connectivity, metabolic imaging, or conventional task-based fMRI.

There is a growing evidence that the fluctuations in the strength of correlations between regions varies throughout the time of a single scan and is likely an aggregate representation of the faster neuronal network reconfiguration. Results from computational modeling suggest that these fluctuations reflect the brain's exploration of the space of potential network configuration [10]. Like traditional connectivity analyses, the characterization of these fluctuations should reflect changes that occur with aging and neuropsychiatric disorders, yet offers a richer description of the dynamic systems-level behavior of the brain [2]. Our approach is to characterize these fluctuations from aggregate fMRI activity using link clustering [11], which allows nodes to belong to multiple communities, in contrast to traditional community detection algorithms.

## METHODS

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org. The sample included 42 subjects (21 AD and 21 controls, matched by age and gender), mean age = 74 (56-86). This sample includes the first MRI occasion of all AD subjects who have usable 3T resting state fMRI scans and a matched group of controls.

Scans were processed using software from FSL[12], FreeSurfer [13] and AFNI [14]. Data were corrected for motion using FSL MCFLIRT [15]. Despiking, regression of time series motion parameters and the mean signal for CSF and white matter, and three dimensional spatial smoothing with a 3mm sigma was performed. We used the mean timecourses from 10mm spheres centered at Montreal Neurological Institute (MNI) coordinates from a previous partitioning of fMRI data into functional nodes [16] to create connectivity graphs (using the Pearson correlation of the timecourses, subtracted from 1.0, as a distance metric).

We used a link clustering algorithm [17], implemented using the linkcomm library [17] to cluster graph edges (links) based on their similarity, a method that allows nodes to belong to multiple communities, reflecting their changing dynamic function. We use a bootstrap resampling approach to determine statistical significance of outcome statistics from the link clustering by drawing 500 random samples of 10 subjects from each group, creating mean connectivity graphs for each group, computing the link clustering and outcome statistics of group differences. We then compared these outcome statistics using a t-test.

**Table 1:** Significant differences between AD and normal subjects on link clustering outcome statistics (500 bootstrap samples in each group).

| | AD | | Normal | | | |
|---|---|---|---|---|---|---|
| | M | SD | M | SD | *t*() | *p* |
| Number of communities | 16.482 | 16.674 | 21.114 | 18.398 | -4.172 | < .001 |
| Number of nodes in the largest community | 243.498 | 12.284 | 240.794 | 14.921 | 3.128 | 0.002 |
| Community centrality | 3.104 | 1.358 | 3.510 | 1.496 | -4.490 | < .001 |
| Number of communities that include the most frequently occurring node | 7.348 | 3.989 | 8.200 | 4.460 | -3.184 | 0.002 |
| Mean distance within all of the communities (mm) | 66.738 | 3.541 | 68.183 | 2.880 | -7.079 | < .001 |
| Mean distance for largest community (mm) | 70.872 | 0.641 | 71.534 | 0.891 | -13.499 | < .001 |

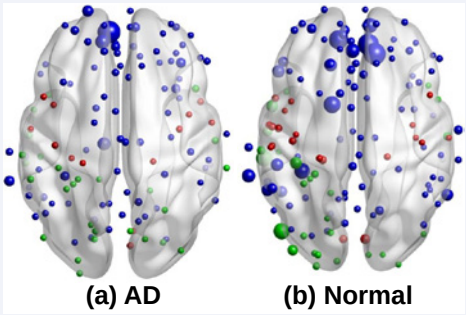


**Figure 1** Differences in the frequencies of nodes that occur in the most communities (dorsal view). The ball sizes are scaled by frequency and the colors represent heteromodal (blue), unimodal (red) and primary (green) cortical association regions. Distribution of the most frequently occurring nodes in normal subjects recapitulates default mode network.

(a) AD subjects show a breakdown of default mode network and disproportionate community participation of the left anterior paracingulate cortex (red arrow).

(b) The distribution of nodes that occur in the largest number of communities reflects the default mode network, without as much reliance on the anterior cingulate cortex. These data were visualized using BrainNet Viewer [18].

## RESULTS

Several outcome statistics of interest from link clustering were significantly different between groups (Table 1), revealing differences in the overlapping community structure of the brain that cannot be quantified with traditional graph metrics. AD subjects have fewer communities with less differentiation, and their nodes belong to less highly connected communities. The left anterior paracingulate cortex (medial frontal wall), an important region in the default mode network, appears disproportionally frequently in communities in subjects with AD compared to normal subjects (Figure 1a). In normal subjects, other nodes are also involved in multiple communities with frequencies that recapitulate the default mode network (Figure 1b).

## DISCUSSION

Alzheimer dementia has been analyzed by some authors as a disconnection syndrome [19], reflecting a disturbance of interactions between multiple neuronal systems as a result of AD pathology. Network analysis techniques have been useful in characterizing salient features of this disturbance; for example, networks appear more randomized, reflecting a global reduction of long distance links between regions [20]. This may be interpreted as a loss of complexity [21].

Our findings are consistent with the literature; specifically we find a significant reduction in the mean distance within all communities and within the largest community. We observe that the mean number of communities is lower in AD and the number of nodes in the largest community is greater, reflecting a less complex pattern of reorganization. The left medial frontal wall, an area that is left relatively intact in AD disease progression [22], is overrepresented in communities in AD, perhaps compensating for other regions in the default mode network that are no longer communicating effectively. These results show that the link clustering approach holds promise for highlighting differences in the dynamic reorganization of networks.

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## REFERENCES

1. Chang C, Glover GH. Time-frequency dynamics of resting-state brain connectivity measured with fMRI. Neuroimage. 2010; 50: 81-98.
2. Jones DT, Vemuri P, Murphy MC, Gunter JL, Senjem ML, Machulda MM, et al. Non-stationarity in the "resting brain's" modular architecture. PLoS One. 2012; 7: e39731.
3. Smith SM, Miller KL, Moeller S, Xu J, Auerbach EJ, Woolrich MW, et al. Temporally-independent functional modes of spontaneous brain activity. Proc Natl Acad Sci U S A. 2012; 109: 3131-3136.
4. Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, et al. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A. 2006; 103: 13848-13853.
5. Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, et al. Disruption of large-scale brain systems in advanced aging. Neuron. 2007; 56: 924-935.
6. Grady CL, Protzner AB, Kovacevic N, Strother SC, Afshin-Pour B, Wojtowicz M, et al. A multivariate analysis of age-related differences in default mode and task-positive networks across multiple cognitive domains. Cereb Cortex. 2010; 20: 1432-1447.
7. Grady CL, Furey ML, Pietrini P, Horwitz B, Rapoport SI. Altered brain functional connectivity and impaired short-term memory in Alzheimer's disease. Brain. 2001; 124: 739-756.
8. Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci U S A. 2004; 101: 4637-4642.
9. Wang K, Liang M, Wang L, Tian L, Zhang X, Li K, et al. Altered functional connectivity in early Alzheimer's disease: a resting-state fMRI study. Hum Brain Mapp. 2007; 28: 967-978.
10. Deco G, Jirsa VK, McIntosh AR. Emerging concepts for the dynamical organization of resting-state activity in the brain. Nat Rev Neurosci. 2011; 12: 43-56.
11. Ahn YY, Bagrow JP, Lehmann S. Link communities reveal multiscale complexity in networks. Nature. 2010; 466: 761-764.
12. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. NeuroImage. 2012; 62: 782-90.
13. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A. 2000; 97: 11050-11055.
14. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res Int J. 1996; 29: 162–173.
15. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage. 2002; 17: 825-841.
16. Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, et al. Functional network organization of the human brain. Neuron. 2011; 72: 665-678.
17. Kalinka AT, Tomancak P. linkcomm: an R package for the generation, visualization, and analysis of link communities in networks of arbitrary size and type. Bioinformatics. 2011; 27: 2011-2012.
18. Xia M, Wang J, He Y. BrainNet Viewer: a network visualization tool for human brain connectomics. PLoS One. 2013; 8: e68910.
19. Delbeuck X, Van der Linden M, Collette F. Alzheimer's disease as a disconnection syndrome? Neuropsychol Rev. 2003; 13: 79-92.
20. Sanz-Arigita EJ, Schoonheim MM, Damoiseaux JS, Rombouts SA, Maris E, Barkhof F, et al. Loss of 'small-world' networks in Alzheimer's disease: graph analysis of FMRI resting-state functional connectivity. PLoS One. 2010; 5: e13788.
21. Stam CJ, Jones BF, Nolte G, Breakspear M, Scheltens P. Small-world networks and functional connectivity in Alzheimer's disease. Cereb Cortex. 2007; 17: 92-99.
22. Brun A, Englund E. Regional pattern of degeneration in Alzheimer's disease: neuronal loss and histopathological grading. A. Brun & E. Englund. Histopathology 1981; 5; 549-564. Histopathology. 2002; 41: 37-38, discussion 38-9.

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