NEURONAL NETWORKS ARE DIFFERENTIALLY AFFECTED IN MUTATION CARRIERS VERSUS NON-CARRIERS IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE

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BACKGROUND

- Autosomal dominant Alzheimer's disease (AD) is caused by known genetic mutations. It is characterized by amyloid accumulation and dementia onset at or around the age of parental dementia onset.[1]
- Dementia onset likely coincides with neurodegeneration, including loss of neuronal networks,[2] but network changes remain incompletely characterized.
- The Dominantly Inherited Alzheimer Network (DIAN)[3] provides a unique population to study how neuronal networks change in individuals with autosomal dominant AD. Characterizing neuronal connections in individuals who will develop AD due to genetic mutations can provide insight into how neuronal networks change in the form of AD (late onset) not caused by mutation carriage.

OBJECTIVES

We performed connection-wise analysis of neuronal networks based on mutation status, cognitive status, and estimated years to symptom onset (EYO) in autosomal dominant AD in order to:

- Determine the effectiveness of threshold-free network-based statistics (TFNBS)[4] in characterizing neuronal networks using diffusion imaging data
- Examine neuronal network differences between mutation carriers and non-carriers as well as those who are cognitively unimpaired and cognitively impaired

METHODS

- Cross-sectional diffusion tensor imaging (DTI) data from 226 DIAN participants were used in this analysis. DTI scans were acquired on 3T Siemens MR scanners with one reference volume and 64 diffusion directions at 2.5mm isotropic voxel size, echo time = 87ms, repetition time = 11000 ms.
- DTI pre-processing was performed using FSL and MRtrix3[5]. Network node regions were identified using the IIT-Desikan gray matter atlas and the ANTs program (**Figure 1**).
- TFNBS method (**Figure 2**) was applied to test the effect of group and the linear interaction effects of EYO and group on neuronal networks.
- EYO was calculated as follows. At any visit:
  - EYO = visit age – mean mutation age of symptom onset (if individual mutation type and mean mutation age of symptom onset is known) OR
  - EYO = visit age – parental age of symptom onset
- Age and sex were used as nuisance variables.
- The following groups were examined:
  - Mutation carriers with AD (AD:MC)
  - Cognitively unimpaired mutation carriers (CU:MC)
  - Cognitively unimpaired non-carriers (CU:NC)

FIGURES & TABLES

Table 1. Sample characteristics.

Group	Cognitively unimpaired non-mutation carriers (CU:NC)	Cognitively unimpaired carriers (CU:MC)	Cognitively impaired (Alzheimer's disease) mutation carriers (AD:MC)
Sample size	n=94	n=100	n=32
Age (years)[a]	39.5 ± 11.3	35.3 ± 9.3	47.2 ± 8.8*
Sex and age (years)	Female (n=62; age = 39.5 ± 11.5) Male (n=32; age = 39.9 ± 11.3)	Female (n=60; age = 36.3 ± 9.6) Male (n=40; age = 33.7 ± 8.7)	Female (n=19; age = 45.8 ± 8.7) Male (n=13; age = 49.2 ± 8.9)
EYO (years)	-9.1 ± 11.3	-14.0 ± 8.4	3.9 ± 2.6

[a]One-way ANOVA with planned contrasts was used to compare mean age differences between groups.
Values shown as mean ± standard deviation. Abbreviations: EYO = estimated years to symptom onset.

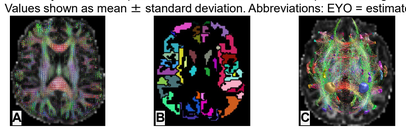


Figure 1. Axial slices of the (**A**) fiber orientation distribution (FOD) map of one subject and (**B**) the IIT Desikan atlas registered to the same subject's native space. The FODs are used to derive structural connectivity between different node regions from an atlas via tractography (**C**), resulting in a connectograph per subject (see **Fig. 2**).

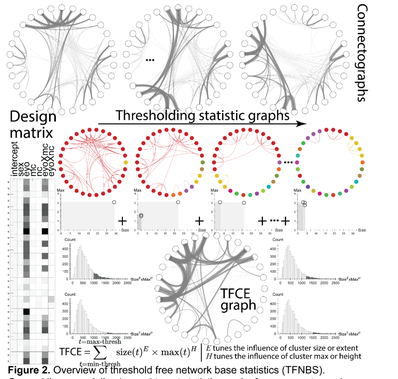


Figure 2. Overview of threshold free network base statistics (TFNBS). General linear modeling is used to get statistic graphs from connectographs. The statistic graphs are thresholded at different thresholds to cluster the connections. The product of size and max of the clusters are summed across the thresholds to obtain threshold free cluster enhanced (TFCE) statistic graph. The null distribution can be obtained for each connection or maximum across the connections using permutation testing. Comparing each connection in the unthresholded statistic graph with (1) max-null or (2) connection specific null, distributions can provide family wise error corrected or uncorrected p-value graphs respectively. For example, **Figs. 3, 4** show uncorrected graphs.

Figure 3. Connectogram demonstrating weighted cross-sectional fiber connections between each brain region examined. Here, the blue lines represent the slope differences in weighted total counts between each fiber region when contrasting AD:MC to the CU:NC group. The darker blue lines indicate connections where the slopes are higher between each region for AD:MC group than in the CU:NC group.

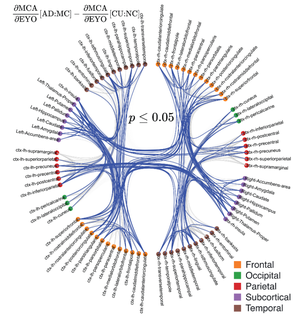
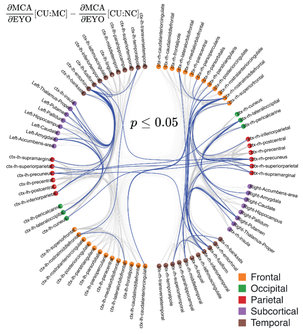


Figure 4. Connectogram demonstrating weighted cross-sectional fiber connections between each brain region examined. The blue lines represent the slope differences in weighted total counts between each fiber region when contrasting CU:MC to the CU:NC group. The darker blue lines indicate connections where the slopes are higher between each region for CU:MC group than in the CU:NC group.



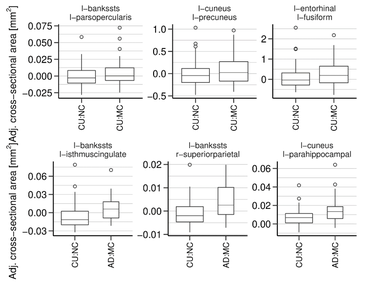


Figure 5. Standard boxplots showing the mean group level differences in cross-sectional area for neuronal network connections with the lowest p-value ≤ 0.05. The cross-sectional areas shown were adjusted for linear effects of age and sex level averages. The connected gray matter nodes are named above each plot. The cross-sectional area of the neuronal connection bundles is larger for mutation carriers.

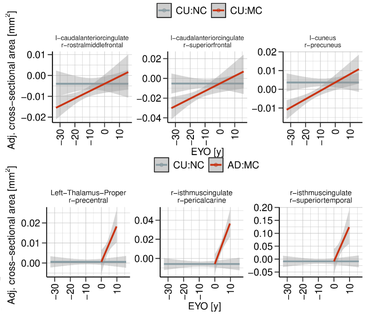


Figure 6. Relationships between estimated years to symptom onset (EYO) and network edges by groups. These graphs show the slopes of ordinary least squares linear fits to the data (after adjusting the cross-sectional area for sex and group specific means) and the 95% confidence intervals of their predictions. These depict the relationships between EYO and the cross-sectional areas of six different pathways that had the lowest p-value ≤ 0.05.

RESULTS

- There were similar numbers of participants in the CU:NC (n=94) and CU:MC (n=100). AD:MC group had the lowest number of participants (n=32). AD:MC group is older than the other two groups, t(223)=5.06, p<.001. See Table 1 for information on other sample characteristics.
- Threshold-free network-based *t*-statistics showed that the percent of edges affected is larger in mutation carriers. Specifically, it is larger in the AD:MC group vs CU:NC group (Figures 2 and 4), and in the CU:MC vs CU:NC groups.
- Weighted total counts, derived from TFNBS statistics, are a proxy of the intra-axonal cross-sectional area of fiber bundles. Figure 3 showed that within cognitively unimpaired participants, the slope of weighted total counts of fiber bundles was greater in mutation carriers than non-carriers.
- As individuals approached EYO, AD:MC group showed larger weighted counts in edges of connections examined that were significant (Figure 5).

CONCLUSIONS

- Our preliminary analyses showed that mutation carriers (both AD:MC and CU:MC groups) had higher intra-axonal cross-sectional area of fiber bundles. We observed a similar increase in intra-axonal cross-sectional area as CU:MC group approached EYO.
- Increased cross-sectional area as EYO approached 0 (i.e., the time of symptom onset) may reflect loosening and shortening of fiber bundles with disease progression.
- Future studies will examine these patterns among individuals with late onset AD and assess longitudinal relationships.

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ACKNOWLEDGEMENTS

This research is supported by NIH grants: 1R01AG059312 (VS/BBB), P50 AG033514 (SA), the Waisman Intellectual and Developmental Disabilities Research Center U54-HD090256, and the Dominantly Inherited Alzheimer Network at Washington University in St. Louis. Thank you to the dedicated research participants who made this research possible.

DIAN
Dominantly Inherited Alzheimer Network

Wisconsin ADRC is funded through the NIH National Institute on Aging and combines academic, clinical, and research expertise from the University of Wisconsin School of Medicine and Public Health and the Geriatric Research, Education, and Clinical Center (GRECC) of the William S. Middleton Memorial Veterans Hospital. For more information: www.adrc.wisc.edu.

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