Regional gray matter volume and default mode network connectivity are associated with age relative to parental symptom onset in sporadic Alzheimer’s disease

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**Background and objectives**

- In autosomal dominant Alzheimer’s disease (AD) mutations, individuals demonstrate increasing abnormality in AD-related biomarkers as they approach their parent’s age of symptom onset. This paradigm has never been tested in sporadic AD.
- AD is characterized by regionally-specific gray matter degeneration, as well as alterations in resting state functional connectivity (rsFC). The default mode network appears especially vulnerable to AD, especially early in the disease process.
- We test whether time till parental symptom onset (tPSO) is associated with abnormality in regional gray matter density (GMD) and rsFC in individuals with a parental history of sporadic AD.

**Image Processing**

**Structural (n=270)**
- Segmentation SPM12
- Non-linear registration to MNII-ICBM152 template
- Smooth with fmm*

**Functional (n=170)**
- Functional parcellation using BASC on 197 young controls
- GLM Connectome to test effect of tPSO on rsFC
- Using DARTEL toolbox
- nIAK
- Sensorimotor and Visual
- Limbic and visual
- MNI-ICBM152 template

**GMD and within-DMN rsFC are reduced as individuals approach parental onset age**

- Gray matter density
  - -5 -2.2 5
  - W-score
  - IPsO (years)
  - Within-DMN functional connectivity
    - 0 -0.5

**Effect of tPSO on GMD**

Gray matter density decreased significantly as individuals approached their parental age of symptom onset, covarying for age, gender, total intracranial volume and ApoE status. Affected regions included the medial prefrontal cortex (mPFC), posterior cingulate, right later temporal cortex, thalamus, and basal forebrain, and overlapped substantially with the default mode network.

**Effect of tPSO on rsFC**

As individuals approached their parent’s age of symptom onset, connectivity decreased within the default mode network, and increased between the limbic and visual networks ((FDR <0.05), controlling for age, gender, motion and ApoE). The observed effects were independent of parental age of symptom onset, covarying for age, gender and total intracranial volume.

**Summary and Conclusions**

- Gray matter density and resting state functional connectivity were found to be more abnormal the closer individuals were to their parent’s age of symptom onset. This is the first study to demonstrate this effect in sporadic Alzheimer’s disease.
- Consistent with the pathological signature of early Alzheimer’s disease, the observed effect was greatest within the default mode network.
- The observed effects were independent of ApoE, suggesting the gene cannot fully explain disease risk conferred by parental history of AD.
- The observed similarity between certain resting state connectivity networks and the pattern of atrophy provides further evidence that gray matter degeneration may propagate through functional networks.