

# Effects of Apolipoprotein E-epsilon 4 Genotype on the Functional Brain Networks Implicated in Cognition in Healthy Middle-Aged Adults

J. Goveas<sup>1</sup>, C. Xie<sup>2,3</sup>, G. Chen<sup>2</sup>, W. Li<sup>2</sup>, B. Ward<sup>2</sup>, G. Chen<sup>2</sup>, J. Jones<sup>4</sup>, M. Franczak<sup>4</sup>, P. Antuono<sup>4</sup>, and S-J. Li<sup>2</sup>

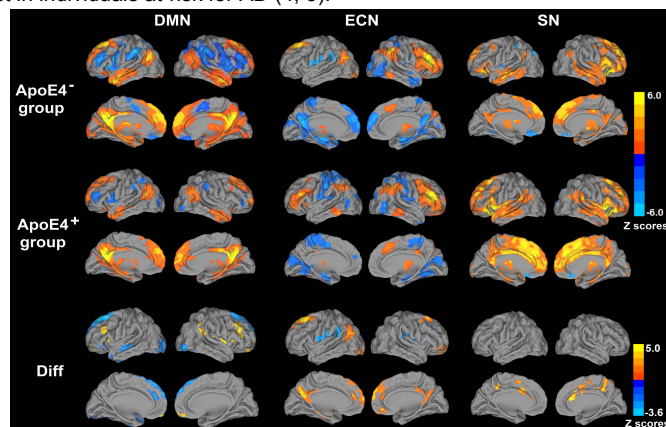
<sup>1</sup>Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin, United States, <sup>2</sup>Biophysics, Medical College of Wisconsin, Milwaukee, Wisconsin, United States, <sup>3</sup>Neurology, School of Clinical Medicine, Southeast University, Nanjing, Jiangsu, China, People's Republic of, <sup>4</sup>Neurology, Medical College of Wisconsin, Milwaukee, Wisconsin, United States

**Introduction:** Apolipoprotein E-ε4 (ApoE-ε4) carriers are at an increased risk for incident late-onset Alzheimer's disease (AD). While diminished default mode network (DMN) functional connectivity is observed in AD, increased DMN connections to medial and dorsolateral prefrontal cortices and medial temporal lobe regions, and decreased connectivity to precuneus are reported in ApoE-ε4 carriers (1, 2). We examined if ApoE-ε4 carriers will show alterations in the DMN, executive control (ECN) and salience networks (SN), relative to ApoE-ε4 non-carriers (3).

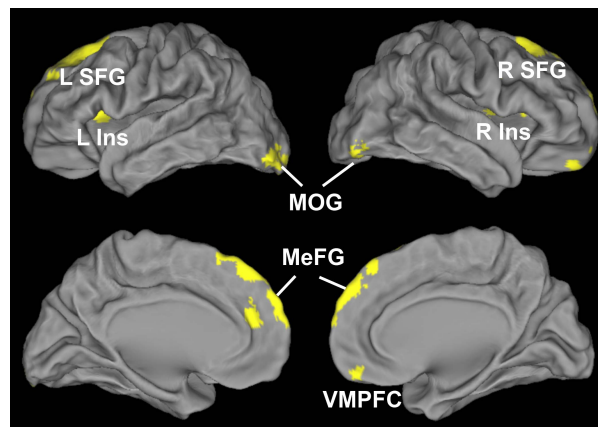
**Methods:** A total of 46 middle-aged, cognitively healthy (CN) subjects aged 44 - 65 years were enrolled in this IRB-approved study. All subjects underwent neurological examination and neuropsychological testing, and DNA samples were collected for ApoE genotype analysis. Written informed consent was obtained from each subject. A series of preprocessing steps common to most functional connectivity fMRI analyses was conducted, using the Analysis of Functional NeuroImages software. Using resting-state functional connectivity (fcMRI) analysis, similarities and differences in the DMN (seed ROI: posterior cingulate), ECN (dorsolateral prefrontal cortex) and SN (fronto-insula) in 20 ApoE-ε4 carriers were compared to 26 non-carriers. Conjunction analysis was performed to find the overlap regions among three networks (DMN, ECN, and SN) based on the differential connectivity between ApoE-ε4 carriers and ApoE-ε4 non-carriers. Subsequently, we quantitatively measured the intrinsic functional connectivity (fc) alterations in these overlap regions between ApoE-ε4 carriers and ε4 non-carriers, in each of these networks.

**Results:** Compared to ε4 non-carriers, ApoE-ε4 carriers showed significant differences in the DMN and ECN in several frontal, temporal and subcortical structures. In the salience network, ApoE-ε4 carriers showed increased functional connectivity (fc) in the dorsal anterior cingulate, posterior cingulate cortex and precuneus (**Figure 1**). Conjunction analysis revealed that in the ApoE- ε4 carriers, alterations in the bilateral middle occipital (MOG), medial and superior frontal gyri (MeFG and SFG), insula (Ins) and ventromedial prefrontal (VMPFC) cortices were present in both DMN and ECN, relative to noncarriers (**Figure 2**). While ApoE-ε4 carriers showed diminished fc in the bilateral middle occipital, medial and superior frontal gyri, increased fc in the insula and ventromedial prefrontal cortex was observed in the DMN. The patterns in the ECN were opposite to that observed in the DMN (**Figure 3**). We did not find any overlap regions between SN and the other 2 cognitive (DMN and ECN) networks.

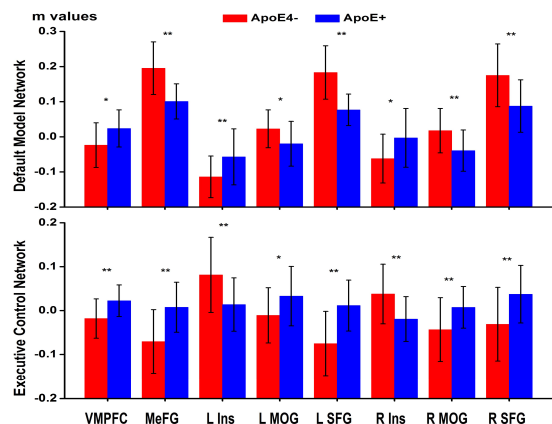
**Conclusions:** Even before onset of cognitive decline, intrinsic fc differences in the brain networks implicated in cognition are seen in middle-aged individuals with genetic risk for AD. Interestingly, most of these brain regions are areas where amyloid and neurofibrillary tangle deposition is seen the earliest in individuals at-risk for AD (4, 5).



**Figure 1.** Network pattern and differences of DMN, ECN, and SN in ApoEε4<sup>-</sup> and ApoEε4<sup>+</sup> groups. Note: Bright color indicates positive connectivity and blue color indicates negative connectivity in ApoEε4<sup>-</sup> and ApoEε4<sup>+</sup> groups, but in the difference (bottom), bright color indicates increased connectivity and blue color indicates decreased connectivity in ApoEε4<sup>+</sup> group compared to ApoEε4<sup>-</sup> group.



**Figure 2.** Overlap regions of the difference of intrinsic connectivity in DMN, ECN, and SN between ApoEε4 carriers and non-carriers. Conjunction analysis found the overlap regions in the DMN and ECN, but did not find the overlap regions in the SN and DMN, or SN and ECN.



**Figure 3.** Quantitative measures of the functional connectivity alteration in the overlap regions of DMN, ECN, and SN between ApoEε4 carriers and non-carriers. \*, p < 0.05; \*\*, p < 0.01.

## References

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## Acknowledgments

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