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### Sex differences of APOE neuropathology-based scores in brain aging

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#### Abstract Text:

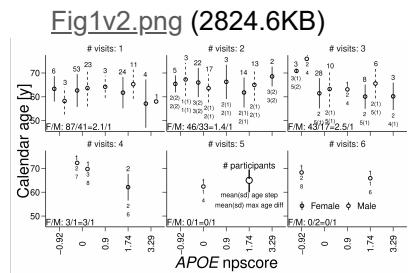
**Background:** By reinterpreting the difference between a model prediction and calendar age, machine learning algorithms allow for estimation of "brain age" using MRI. There is growing evidence for sex differences in the influence of APOE genotype (evaluated as APOE ε4 carrier status) on Alzheimer's disease (AD) endophenotypes at various stages of disease. The purpose of this study is to examine the influence of an APOE neuropathology-based score (APOE npscore) on the brain aging estimated from deep learning.

**Methods:** Brain age from 274 participants (**Fig. 1**) in the Wisconsin-ADRC was estimated from T1w-MRI using a publicly available deep learning model called two-stage-age-network (TSAN) that was pre-trained on over four thousand scans from OASIS, ADNI-I and PAC-2019. TSAN uses a novel rank-based loss along with mean squared loss and makes predictions in two steps which does not require *a posteriori* bias correction. This is a significant improvement from prior deep learning models in reducing the "regression-to-mean bias" typically present in brain age models. APOE genotypes ( $\epsilon 2\epsilon 2$ ,  $\epsilon 2\epsilon 3$ ,  $\epsilon 3\epsilon 3$ ,  $\epsilon 2\epsilon 4$ ,  $\epsilon 3\epsilon 4$ ,  $\epsilon 4\epsilon 4$ ) were weighted by the log(odds-ratio) from a large study of autopsy-confirmed AD cases/controls, providing a variable representing the relative amount of risk across APOE genotypes. Mood's median test was used to examine the sex differences between the excess brain aging (EBA) as a function of the APOE npscore.

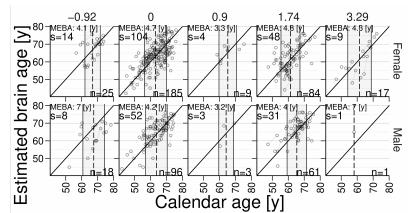
**Results:** **Fig. 2** shows the brain age predictions. **Fig. 3** shows that there are significant differences between females and males in the EBA for the APOE npscore <0. Median EBA for both males and females is <0 when APOE npscore <0 suggesting protective effects of ε2 on brain aging. The median EBA >0 for both the sexes when APOE npscore ≥0.

**Conclusion:** We report sex differences in the influence of APOE genotype on brain aging. There is heterogeneity in the differences within the ε4+ (APOE npscore >0) and ε4- (APOE npscore ≤0) groups. These sex differences may not be observed when using just ε4 carrier status instead of the APOE npscore. This provides evidence for a shift in paradigm for the way we analyze APOE genotype because of latent nuances of the ε4-status influence on AD outcomes.

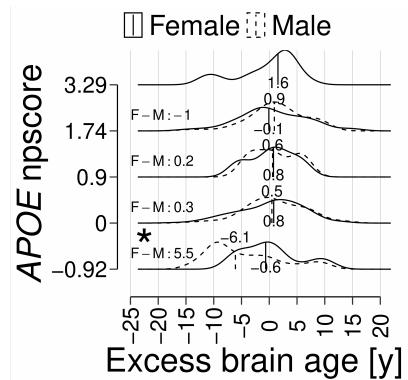
#### Tables and Figures:



**Figure 1.** Basic demographics and study sample information. Mean and standard deviation ( $sd$ ) of calendar age are shown for groups of participants for each APOE npscore and sex with different number of visits. For each group the number of participants, mean and  $sd$  for age step (age gap between the consecutive scans) and max age diff (maximum age gap across different visits). Important to note is that for the repeat scans the age gap between consecutive scans is on average about 2 years. Thus, the dependence among the samples is accounted for by setting the bandwidth of the density estimations (in Fig. 3) to 2 years.



**Figure 2.** Brain age predictions, sample sizes, mean excess brain aging (MEBA) by different groupings of the study samples. Please note that there are repeat scans for some of the participants (Fig. 1), however the bandwidth used for estimating the density of the distributions in Fig. 3 is 2 years which is approximately the age gap between the consecutive repeat scans. The number of participants ( $s$ ) and the number of images ( $n$ ) are shown for each of the group. The mean calendar age (dashed vertical line) and its standard deviation spread (shaded rectangle) are also shown. We can observe that the estimated brain age values are close to the Unit slope and zero intercept line shown for each group.



**Figure 3.** Sex differences in densities of excess brain aging (brain age – calendar age) as a function of the APOE npscore. The density estimates (using a bandwidth of 2 years) of the excess brain age along with the medians are shown. \* $p \leq 0.05$  according to Mood's median test. The median values for females (F) and males (M) for each of the APOE npscore are shown by the vertical lines. The median difference values ( $F-M$ ) are also shown on the left for each APOE npscore.

**Fig2v2.png (4151.5KB)**

**Fig3.png (1245.6KB)**

## Title:

Sex differences of APOE neuropathology-based scores in brain aging

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## Preferred Presentation Format:

Oral Presentation Preferred, but will do Poster Presentation if so assigned

**Was this research funded by an Alzheimer's Association grant?**

No

**Abstract Submission Affirmations:**

I agree to the Abstract Submission Affirmations.

**Do you plan to upload figures or tables to supplement your abstract text?**

Yes

**Theme:**

Biomarkers

**Topic:**

Neuroimaging

**Sub Topic:**

Imaging and genetics

**Learning Objectives:**

Recognize the importance of using APOE neuropathology-based score when studying APOE genotype effects on imaging based aging biomarkers in AD.

**Keywords:**

APOE, Alzheimer's disease and magnetic resonance imaging (MRI)

**Fellowship:**

No.

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Signed on 01/26/2022 by *Nagesh Adluru*

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