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Disappearing metabolic youthfulness in the cognitively impaired female brain

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ABSTRACT

Sex differences play a vital role in human brain structure and physiology. Previous reports have proposed evidence hinting at a metabolic advantage in female brains across adulthood. It remained to be determined whether this advantage would be maintained across the spectrum of cognitive impairment, up to and including dementia due to Alzheimer's disease (AD). Here, using a machine-learning algorithm, we explore sex differences in metabolic brain-age derived from fluorodeoxyglucose positron emission tomography imaging among cognitively healthy individuals and those affected by mild cognitive impairment and clinically probable AD. First, we report that cognitively healthy male participants showed a persistently "older" looking brains when compared to healthy female participants in term of metabolic brain age, confirming earlier reports. However, this distinction disappeared among MCI individuals and probable AD patients, and this loss could not be explained by an accompanying neurodegeneration. This would seem to indicate that females have a higher rate of decline in brain glucose metabolism when cognitively impaired to negate their prior advantage.

1. Introduction

Goyal et al. have reported that cognitively healthy females (CH-F) have brains that appear significantly more "youthful" in terms of metabolism than comparable males (CH-M) across the lifespan (Goyal et al., 2019). In their study, Goyal et al. used quantitative positron emission tomography (PET) regional total glucose use, oxygen consumption, and cerebral blood flow, coupled with machine-learning algorithms, for estimating metabolic brain age (Goyal et al., 2019). In this framework, a negative difference in brain age with respect to the individual's life chronology is indicative of a "younger-appearing" brain. Their hypothesis to explain this finding is that females retain, for a longer period, neotenous features.

There were a number of counter-arguments to this report that were raised by Biskup et al. (2019) as well as Tu et al. (2019). One objection centered on the notion of the results expressing true neotenous processes and/or aerobic glycolysis. Indeed, caution must be taken in the interpretation of brain age differences, as they are simply expressions of a relative, statistical likelihood between the individual's image(s)/measurement(s) and the training set, not direct and absolute expressions of any specific biochemical differences. All authors were in agreement that the specific neotenous hypothesis would need further demonstrations. A second objection was the inability of the model to predict an individual's sex a posteriori. This is slightly misguided, as the machine-learning model was trained to select features sensitive to age, not to sex differences; therefore, any attempt to be specific at sex prediction was doomed to fail. A third point of contention was the selective nature of regional metabolic differences. In their report, Goyal et al. demonstrated that sex differences were more dependent on brain glucose use than blood flow or oxygen consumption. Speaking to this result, we and others (Herholz et al., 2002; Hsieh et al., 2012) can confirm a general decline in glucose uptake throughout the brain with aging, which is, however, not entirely explained by sex differences. In recent work we studied fluorodeoxyglucose (FDG) PET data, a technique which monitors labeled glucose uptake, and therefore serves as a relative indicator of brain glucose use. We established normative metabolic results on 802 cognitively healthy (CH) individuals aged 20–94 years old and showed that the effect of sex, while significant, explained less than 2% of the variance—less than scanner resolution, for example (Nugent et al., 2019).

The largest issue raised in Goyal et al. was that the trajectory of sex differences in brain metabolism should be explored in the

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Table 1
Participants demographic data

Group	CH-M	CH-F	MCI-M	MCI-F	AD-M	AD-F
N	274	274	220	220	146	146
Age, mean ± SD	71.81 ± 7.31	71.94 ± 7.27	72.68 ± 8.07	72.32 ± 7.98	74.00 ± 7.16	74.19 ± 6.98
Age range	52–91	51–94	54–89	55–90	55–92	56–91
MMSE, mean± SD	29.10 ± 1.17	29.28 ± 1.03	27.83 ± 1.72	28.00 ± 1.78	23.30 ± 2.99	23.15 ± 3.51

AD, Alzheimer's disease; CH, cognitively healthy; F, females; M, males; MCI, mild cognitive impairment; MMSE, mini-mental state examination; N, number; SD, standard deviation.

context of neurodegeneration, such as that due to Alzheimer's disease (AD). There is evidence showing that FDG-PET glucose uptake declines before measurable cognitive impairment due to AD (Scheef et al., 2012), to eventually affect the hippocampus, posterior cingulate cortex, and parieto-temporal cortical regions of the brain in AD (Herholz et al., 2002; Hsieh et al., 2012). Further, females are not only at considerably greater risk of AD, but also deteriorate cognitively faster than males at equivalent disease stages, as defined by a combination of biomarker and clinical diagnostic levels (Sohn et al., 2018). It should be noted that females might exhibit a higher pathological load at equivalent cognitive status when compared to males, indicative of increased cognitive resilience to pathology (Arenaza-Urquijo et al., 2019; Armstrong et al., 2019; Buckley et al., 2018; Buckley et al., 2019). This suggests that sex should be regarded as a major risk factor and be further explored in this context.

In this work, we aimed first to confirm the female brain metabolic youthfulness results of Goyal et al. by investigating brain age in CH individuals using FDG-PET glucose uptake, our own algorithm for brain age, a correction factor for regression dilution, and a twice larger, different cohort of 548 CH participants. We then investigated whether this metabolic "youthfulness" advantage in females remained in the presence of neurodegeneration and cognitive impairment in an additional cohort of 732 MCI and probable AD patients. We showed that although females exhibited a significant metabolic brain age "youthful" advantage in adulthood, it disappeared in the presence of neurodegeneration and cognitive impairment.

2. Material and methods

2.1. Participants

This study was conducted on a sample of 1453 participants acquired from the Alzheimer's Disease Neuroimaging Initiative, Open Access Series of Imaging Studies, Banner Alzheimer's Institute, Alzheimer's Disease Repository Without Borders, and the Centre Hospitalier Universitaire de Sherbrooke. We randomly sampled participants from all studies to ensure a similar age distribution between females and males in each clinical group (CH, MCI, and AD). Therefore, 1280 participants were included in our final analysis. The sample was divided into 6 groups, using self-reported sex at birth and according to established clinical diagnostic guidelines and neuropsychological assessment tools for AD. Participants demographic data are presented in Table 1. There were no significant differences between males and females in either CH, MCI, and AD groups in terms of chronological age (CH: p= 0.83, MCI: p= 0.63, AD: p= 0.81) or Mini-Mental State Examination (CH: p= 0.07, MCI: p= 0.63, AD: p= 0.32).

2.2. Image processing

FDG-PET that did not have a corresponding anatomical magnetic resonance image (T1w MRI) acquired within one year were not included (n = 85). All FDG-PET image preprocessing was performed using the MINC 2.2.00 toolkit: conversion to the MINC2 format, co-registration to the first frame; timeframe averaging (with the exception of Alzheimer's Disease Neuroimaging Initiative FDG-PET, already co-registered to the first frame of the raw image file and timeframe averaged (Jagust et al., 2015)). PET FDG images were then co-registered to their respective T1w MRI and partial volume corrected (PVC) using region-based voxel-wise correction, an extension of the geometric transfer matrix method. PVC was implemented using PETPVC (https://github.com/UCL/PETPVC). Next, PET images were converted to standard uptake value ratios (SUVR) by the voxel-wise division of the average activity of the paracentral cortex, which had been reported as the optimal region for FDG-PET image normalization in normal aging studies (Jiang et al., 2018). Finally, images were smoothed to a uniform resolution of 8 mm full-width half maximum and the parcellated T1w MRI FreeSurfer (Freesurfer.net, *FreeSurfer* 6.0) regions from the Desikan-Killiany-Tourville (DKT) atlas (Klein and Tourville, 2012) were used to extract estimates of SUVR as metabolic brain features. Each brain segmentation was visually inspected through at least 20 evenly distributed coronal sections.

2.3. Metabolic brain age estimation

We employed a standard support vector regression algorithm followed by a linear kernel to predict brain age from FDG-PET SUVR. We initially set out our brain age framework using two-thirds (66%) of CH-F data (N = 182) as a training set, and validated these estimates using 10-fold cross validation. We performed age-dependent bias-correction as described in our previous work to counter the effects of regression dilution (Beheshti et al., 2019).

2.4. Cortical signature of AD

The cortical signature of AD was obtained by computing the mean cortical thickness extracted with Freesurfer of the following regions: entorhinal, inferior temporal, middle temporal, and fusiform cortices (Jack Jr et al., 2015).

2.5. Statistical analyses

We used the CH-F trained brain age model to compute brain age in other samples (i.e., females and males CH, MCI and AD test sets). We reported prediction accuracy based on the coefficient of determination (R^2), the mean absolute error (MAE), root mean absolute error (RMAE), and metabolic brain age difference (i.e., chronological age subtracted from metabolic brain age). Sex differences in terms of metabolic brain age difference were tested using independent t-tests. We tested regression coefficients between males and females in each category as follow (Paternoster et al., 1998):

$$z = \frac{b_m - b_f}{\sqrt{s_{bm}^2 + s_{bf}^2}} \quad (1)$$

where b_m and b_f stand for the slopes, and s^2_{bm} and s^2_{bf} refer to the standard errors related to the male and female regression lines, respectively. We further tested whether the cortical signature of AD could modify the relationship between brain age difference by adding it along with FDG-PET SUVR values to the prediction model. Additionally, we used linear regression to assess whether the interaction terms were significant between age, sex and age × sex on the estimated brain age among different groups (i.e., HC, MCI, and AD). Finally, to verify that brain age prediction was not influenced by the training set, we rebuilt the framework and conducted all experiments anew with the CH-M data as a training set. All machine-learning analyses and statistical tests were conducted in a MATLAB environment. Our source code to compute the brain age values is available at: https://github.com/medicslab/BrainAgeEstimation.

3. Results

3.1. Summary of experiments

We used FDG-PET-driven SUVR followed by a supervised machine-learning algorithm to determine a metabolic brain age with which we explored sex differences among cognitively healthy individuals and those affected by MCI and AD. The brain age framework was built on the basis of a training set of CH-F data and tested on other samples (i.e., females and males CH, MCI, and AD test sets). Furthermore, we assessed the association between metabolic brain age scores and cortical signature of AD among test sets in order to remove the confound of neurodegeneration.

3.2. Computation of metabolic brain age

Brain age estimates were very accurate in a 10-fold cross-validation analysis of the CH-F training set (N = 182, MAE = 2.22 years, RMSE = 2.90 years and R^2= 0.85; mean brain age difference 0.00, 95% confidence intervals (CI) = [−0.42, 0.42] years), with no significant correlation between brain age difference and chronological age (r = 0.00, p = 1). The predictive accuracy of the model in the independent CH-F test set was equally accurate (N = 92, MAE = 2.63 years, RMSE = 3.24 years, R^2 = 0.86; mean brain age difference −0.04, 95% CI = [−0.73, 0.64] years). The correlation between brain age difference and chronological age in the independent CH-F test set was not significant (r = 0.10, p = 0.32).

3.3. Metabolic brain age comparisons on the cognitive spectrum

Using the CH-F training set, Fig. 1 illustrates the relationships by sex between brain age as a function of chronological age; between brain age difference as a function of chronological age; between female and male regression coefficients; and between brain age difference amongst different groups (i.e., HC, MCI, and AD). Of note, CH-M showed a significantly higher mean metabolic brain age difference compared to CH-F (males: 1.16, 95% CI = [0.77, 1.55] years; females: −0.04, 95% CI = [−0.73, 0.64] years; t = 3.02, p< 0.01, *cf.* Fig. 1J). Indeed, in term of metabolic brain age, cognitively health females experienced persistently "younger" looking brains when contrasted with males. In the MCI group, while MCI-M and MCI-F showed a positive mean metabolic brain age difference when compared to CH-F (males = 1.80, 95% CI = [1.37, 2.23] years; females = 1.86, 95% CI = [1.44, 2.28] years, *cf.* Fig. 1E), there was no significant difference between sexes with respect to metabolic brain age difference (t = −0.19, p= 0.84, *cf.* Fig. 1K). A similar situation was observed in the AD group (males = 5.13, 95% CI = [4.57, 5.70] years, females = 4.38, 95% CI = [3.72, 5.03] years, t = 1.73, p= 0.08, *cf.* Fig. 1F and L). Indeed, the metabolic brain age difference in the AD group did not reach statistical significance. There were no significant differences between males and females in either CH, MCI, and AD groups in terms of regression coefficients (CH: p= 0.61, MCI: p= 0.58, AD: p= 0.37). Unlike age (p< 0.001), sex and the interaction age × sex had no significant influence on the estimated brain age results in each group (p> 0.05).

3.4. Effect of neurodegeneration

A possible confound not investigated in Goyal et al. and mentioned by Biskup et al. was to correct for the effect of neurodegeneration. We therefore extracted a weighted average of cortical thickness in specific areas related to AD, the Cortical signature of AD (Jack Jr et al., 2015), to determine if there were correlations between brain age differences and neurodegeneration. We found a significant negative association between brain age difference and Cortical signature of AD among all test samples (r = −0.32, p< 0.001). Yet, when we added the cortical signature as a covariate in the predictive model for brain age, it did not statistically explain the difference in brain age between males and females (mean metabolic brain age delta as follows: CH (males: 1.14, 95% CI = [0.76, 1.51] years; females: 0.05, 95% CI = [−0.59, 0.70] years; t = 2.87, p< 0.01); MCI (males: 1.88, 95% CI = [1.47, 2.29] years; females: 1.93, 95% CI = [1.53, 2.33] years; t = −0.86, p= 0.17); AD (males: 5.38, 95% CI = [4.83, 5.93] years; females: 4.72, 95% CI = [4.08, 5.36] years; t = 1.54, p= 0.12).

3.5. Areas of sex difference

To illustrate sex differences within cortical signature areas, we used the support vector regression weights obtained with the CH-F trained model as a reference (i.e., with a brain age difference of −0.04) and then increased the feature's values in the CH-F trained model to achieve an average metabolic brain age delta at the same level in males (i.e., a brain age difference of 1.16 years). The support vector regression weights' differences between the 2 simulations are shown as a region-wise sex differences map between CH-F and CH-M (Fig. 2). Finally, in order to verify that all of the above prediction results were not particular to the CH-F training set, we rebuilt the brain age estimation framework with a CH-M training set and repeated all tests, which produced similar significant results (see Supplementary Materials for details).

4. Discussion

Our results demonstrate, in accordance with those of Goyal et al., that cognitively healthy female brains in our sample appeared more youthful than males, i.e., possess metabolic features associated with chronologically younger females. We observed however a smaller gap between CH-F and CH-M in terms of delta than in the Goyal study on the basis of a CH-F training set (1.20, 95% CI = [0.45, 1.99] years vs. 2.4 years, both p< 0.05. There are several possible explanations. First, our dataset was larger, and therefore likely more variable; that it is a reflection of our study focusing on older adults (47–94 years old), rather than the full adulthood (20–82 years old). Second, we applied a robust bias-correction scheme (Beheshti et al., 2019) to diminish the oft-reported age dependency from the predicted results. Third, with respect to the Goyal et al. study, it should be noted that used brain metabolism (i.e., PET regional total glucose, oxygen, and aerobic glycolysis), and cerebral blood flow for estimating the brain age. Using these modalities, they documented that sex differences were more dependent on brain glucose use than blood flow or oxygen consumption. In this study, we solely used PET regional total glucose features, which does not allow us to reach the exact same conclusion. Further, Goyal et al. used literature-derived quantitative

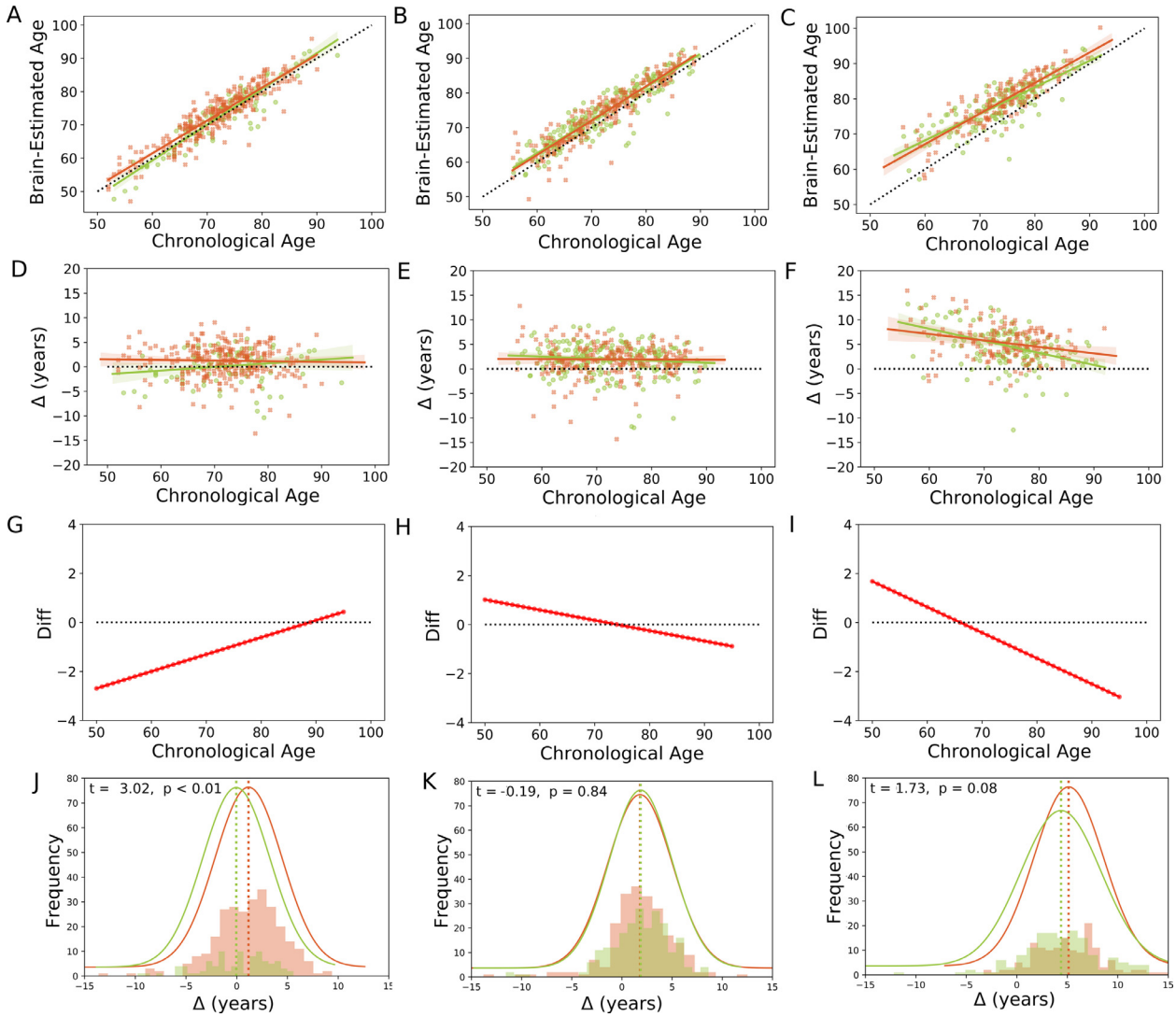

Fig. 1. Sex differences in metabolic brain-age for cognitively healthy participants, either females or males (CH-F, CH-M), as well as individuals with mild cognitive impairment (MCI), and clinically probable Alzheimer's disease (AD). Top row (A, B, and C): Scatter plot of metabolic brain age as a function of chronological age. The identity line (y = x) is shown with the dashed black line. Second row (D, E, and F): Brain age difference (estimated – chronological) as a function of chronological age. Regarding the top row and second row, points indicate females (green spot) and males (orange spots), and lines stand for regression lines for each group (females = green; males = orange). Third row (G, H, and I): Differences between female and male regression lines as a function of chronological age. Bottom row (J, K, and LI): Distributions of brain age difference for each group, with brain age values computed on the basis of a training set of CH-F (females = green; males = orange).

normalization factors to get their metabolic estimates, whereas we used SUVR features which is a semiquantitative method. Finally, Goyal et al. normalized the FDG-PET image using whole brain age-normative data, while we used the paracentral cortex as reference region as it had been reported as ideal region for FDG-PET image normalization on normal aging (Jiang et al., 2018). All of these methodological factors may have an impact in comparing findings from both studies.

Our sex gap was lower than a recent study by Cole which reported 5.58 years younger-appearing brains for CH-F compared to CH-M on the basis on T1w MRI data (Cole et al., 2017). It is important to note that a sex gap on the order of year(s) persists despite differences among these studies, including brain imaging modality (FDG-PET vs. multiparametric PET vs. T1w MRI), machine-learning method (support vector regression vs. random forest vs. Gaussian process regression), and bias correction methods for regression dilution.

In this study, we used a bias-correction scheme developed in priori work (Beheshti et al., 2019), which once applied demonstrated a lower variance in brain age delta values as well as lower MAE after including chronological age in the bias-correction framework (de Lange and Cole, 2020). In order to verify that all of the above prediction results were not influenced by our bias-correction scheme, we generated the brain age values with the alternative bias-correction method suggested by Cole and colleagues (Cole et al., 2017), with more details described elsewhere (de Lange and Cole, 2020). All repeated tests produced similar significant results (see Supplementary Materials for details). However, it should be noted that it is still unclear how bias correction methods affect downstream comparisons between groups and methods for regression dilution correction are controversial, and require ongoing studies (Butler et al., 2020).

Regardless, the difference remains significant, indicative of female brains appearing to achieve and retain a metabolic integrity advantage over males until old age. This difference is not ex-

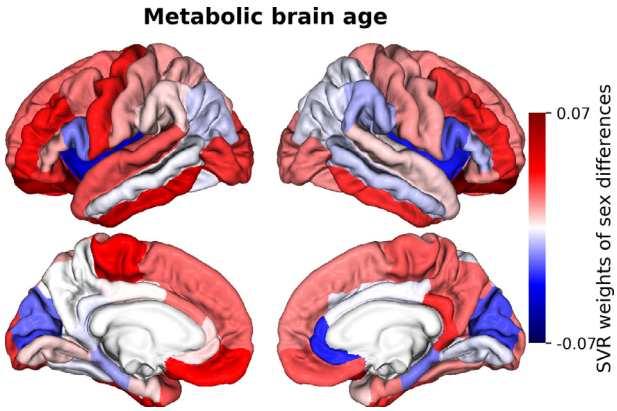

Fig. 2. Support vector regression weights variations related to sex differences between cognitively healthy females and males on the basis of metabolic brain features. The regions with hotter colors represent areas of higher male brain age difference (i.e., male brains were "older" than female's), whereas cold colors represent the reverse (i.e., female brains were "older" than male's).

plained by age-associated neurodegeneration of the cortical mantle, at least not in the regions included in the Cortical signature of AD, and therefore points to specific sex-differentiated processes.

The latter study used cortical thickness as a basis to derive a brain age estimate, much like the work of Cole et al. (Cole et al., 2019) and not unlike our patch-based approach (Beheshti et al., 2019). First, an analysis of the regions subtending the cortical thickness brain age model shows that they are not identical to those involved in metabolic brain age. Second, it is quite possible that a more "mature" cortical mantle (i.e., dendritic-rich, synaptically pruned, and with more advanced myelination), accedes to a more efficient metabolic homeostasis, which would be construed in an adulthood model as "younger."

In the presence of cognitive impairment, however, these trends are not maintained. By the time the functional brain is cognitively impaired, females have lost their metabolic youthful advantage (Fig. 1G). This would imply that females have not retained heightened glycolysis when exhibiting cognitive impairment.

Furthermore, regardless of sex, we observed a greater elevation of metabolic brain age difference in younger MCI/AD participants than older MCI/AD participants (Fig. 1E, F), suggesting that the rate of decline in the brain metabolism in early-onset AD patients is higher than in late-onset AD patients. Our findings are congruent with other studies documenting that early-onset AD suffer from a faster rate of AD progression than late-onset AD patients (Koss et al., 1996).

It is possible that this normalization of metabolic brain age is due to either a sampling or survival bias in males in our sample, or the presence of a male-associated protective trait against the negative consequences of neurocognitive degeneration.

It is more probable that females undergoing neurodegeneration of an Alzheimer's pathological nature have an accelerated rate of decline in brain metabolism, in order to age "faster" than males and obviate the earlier gap. This points us in the direction of a phenomenon that would need to be universal in nature (e.g., hormonal maturation) providing females with a precociously matured cortex compared to males before adulthood, gradually building up a metabolic advantage over approximately a decade during early adulthood, an advantage which would remain for 3–4 decades. In the fifth and sixth decade, a decline in this phenomenon in women of all provenance (e.g., menopause) would similarly lead to a gradual disappearance of this advantage, approximately a decade after its inception, leaving the brain in a vulnerable state for additional insult(s) and possibly leading to cognitive impairment. This combination of effect would therefore explain the observed evidences throughout the female lifespan: an increased cortical age in younger years and a reduced metabolic age throughout adulthood, gradually worsening when in the presence of cognitive impairment and dementia.

However, when we explicitly quantified cognitive impairment between females and males, other factors such as sexual dimorphism, societal factors, co-morbidities (e.g., vascular disease) should be considered. For instance, it has been shown that aging males may have a healthier cardiovascular risk profile, resulting in a lower risk of dementia than females of the same age (Vegeto et al., 2020). We may further speculate whether this is a cue toward explaining the higher incidence of AD-related dementia in females. Future neuroimaging studies with longitudinal outcomes would be most beneficial in advancing our understanding of sex differences in AD.

5. Conclusion

We set out in this study to examine the sex differences among people who suffer from AD in terms of metabolic brain-age. To this end, we used a unique and large sample of 1280 individuals with FDG-PET imaging. Our simulation results showed that, in the clinical groups (i.e., MCI and AD), male brains and female brains showed a similar pattern of decline in terms of the brain glucose metabolism, despite the fact that the healthy female brains appear younger than the healthy male brains.

Author contributions

I.B, O.P, and S.D designed research; S.N performed PET analysis. I.B performed research; I.B, O.P and S.D analyzed data; and I.B, O.P, S.N and S.D wrote the paper.

Consent for publication

Not applicable.

Disclosure statement

The authors declare no competing financial interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2021.01.026.

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