LETTER

# REPLY TO BISKUP ET AL. AND TU ET AL.: Sex differences in metabolic brain aging

Manu S. Goyal[a,b,c,1], Andrei G. Vlassenko[a], and Marcus E. Raichle[a,b,c]

We greatly appreciate the interest and thoughtful insights into our study by both Biskup et al. (1) and Tu et al. (2). Their comments prompted us to further analyze the data published in our paper (3), as discussed below.

Biskup et al. (1) first wonder whether our results might be due to the multiparametric nature of the dataset or, alternatively, could be related to a global difference in rationing between aerobic glycolysis (AG) and oxidative metabolism. We investigate this further by looking at each metabolic parameter independently. First, generalized linear modeling reveals that sex-based differences in regional gray matter AG (adjusted for chronological age) correlate well with how much a region's AG varies with age (i.e., regions with higher AG in females are also those that lose the most AG with age, Pearson's $r = 0.72$), suggesting that more typical statistical analysis for AG alone reflects the results from our multiparametric machine learning model.

Next, we investigated whether sex-based differences in metabolic brain age persist when calculated independently for AG, total glucose use (CMRGlc), oxygen consumption ($CMRO_2$), and cerebral blood flow (CBF). We again find that females (as test cases) have a significantly lower metabolic brain age than males (as training cases) for AG, CMRGlc, and $CMRO_2$, independently, but not for CBF (females vs. males, $t$ test: −5.3 y, $P < 0.005$; −5.1 y, $P < 0.01$; −4.5 y, $P < 0.05$; −0.2 y, $P > 0.8$; respectively; the first three results remain $P < 0.05$ when test-training cases are reversed). These results would suggest that sex differences in metabolic brain aging are a more general phenomenon. This is also reflected in prior studies; for example, it has been found that females undergo an aging transition in brain transcription patterns later than males (4), and brain age prediction based on structural MRI alone in an older cohort was also found to be younger in females than in males (5).

Biskup et al. (1) also remark that females might be more vulnerable to neurodegeneration than males. For example, it has been reported that females with mild cognitive impairment have more neurodegeneration and rapid decline than males (6, 7). This might seem counter to the idea of increased youthfulness in the female brain. However, if one compares females and males at an equivalent cognitive level, then increased neurodegeneration in females could also be interpreted as reflecting increased resilience to neurodegenerative disease, since males with more advanced Alzheimer's disease might not have been included in the comparison due to more advanced symptoms. Importantly, this "resilience bias" explanation (akin to survivorship bias) does not exclude a simultaneously heightened risk to neurodegeneration in females; indeed we propose that "metabolic youth" in the brain—and the decades of relative increase in activity and plasticity that it may reflect—could in fact pose both risks and resilience to neurodegenerative disease. This hypothesis, which others have raised in various forms previously (8–10), is exemplified by an association among AG, lactate production, and amyloid plaque deposition (11, 12), yet a simultaneous protective effect to neuronal survival from glycolysis (13, 14).

Tu et al. (2) question whether potential bias in the 35- to 50-y age group could have affected our finding of lower metabolic brain age in females, a caveat that we also acknowledge in our paper (3). Removing the 35- to 50-y age group when comparing females and males produces nearly identical results (trained on males, $P < 0.003$; or on females, $P < 0.04$). Further data and investigations will be necessary to determine whether sex differences in metabolic brain aging vary by age, particularly before and after menopause. Tu et al. also note that in children and adolescents, a brain age calculated from structural MRI interestingly predicts a slightly lower brain age for boys than girls, arguing against our hypothesis that pubertal effects on brain metabolism might set the stage for the adult differences in our study. However, previously reported cortical CBF changes after puberty in females versus

[a]Neuroimaging Laboratories, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO 63110; [b]Department of Neurology, Washington University School of Medicine, St. Louis, MO 63110; and [c]Department of Neuroscience, Washington University School of Medicine, St. Louis, MO 63110

Author contributions: M.S.G., A.G.V., and M.E.R. designed research, performed research, analyzed data, and wrote the paper.

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[1]To whom correspondence should be addressed. Email: goyalm@wustl.edu.

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males do not agree with their findings (15) and, nonetheless, it is incorrect to assume that changes in brain metabolism will necessarily match changes in brain structure; as we and others have shown, even different components of brain metabolism differ from one another in how they vary with age (16–19).

This fruitful correspondence highlights that how one interprets sex differences in brain aging might be dependent on the data (e.g., structural versus metabolic, or cohort effects), the analysis (e.g., quantitative versus topographic), and one's perspective [e.g., inferential statistics versus predictive machine learning (20)]. This should not dissuade one from doing research on sex differences, but it will remain vital to keep track of these different methods and perspectives when synthesizing and interpreting the data. We eagerly join our colleagues in recognizing the importance of future investigations that help to disentangle sex differences in aging and, more broadly, continue to advocate for a deeper consideration of the complex roles of metabolism beyond simply providing energy for activity in the human brain.


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