LETTER

Sex differences in brain metabolic activity: Beyond the concept of brain age

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We have read the article in PNAS by Goyal et al. (1) with great interest. The identification of underlying organic differences between female and male brains is of utmost importance to reach sex-sensitive precision medicine (2–4).

The main findings of the paper (1), "the female brain has a persistently lower metabolic brain age—relative to their chronological age—compared with the male brain," lend themselves to the conclusion that women's brains are younger than men's. However, we would like to raise a number of considerations that might help revisit the main conclusion of the data presented.

Goyal et al. (1) applied a supervised machine learning algorithm to multiregional, PET-based measurements of brain metabolism of a cohort of 205 participants. By training the algorithm on male data and applying it on female data, the authors noted that female brains appeared to be about 3.8 y younger than their chronological age. Similarly, when trained on female data, the model predicted male brains to be 2.4 y older than their actual age.

Based on their previous findings, the authors concluded that this mismatch is due to the fact that the typical female brain is more youthful—that is, metabolically neotenous—than the male brain. Unfortunately, to the best of our knowledge, the actual differences between male and female neoteny and/or aerobic glycolysis (AG) processes have not yet been established. A few points might help identify alternative interpretations.

First, it should be noted that the metabolic data used for training the model are multiparametric, and AG might not be the most important player in the sex difference observed. Underestimation of women's chronologic age based on a male-trained model might therefore simply indicate a different ratio of AG to oxidative glycolysis between men and women. Sex and gender differences in brain metabolism in general are still very poorly understood (5).

Second, higher female AG might not be necessarily a sign of younger metabolic age. AG takes only a small portion of the entire brain metabolism of the adult brain (10%), and this percentage is subject to variations due to age, as well as to brain regions (6), brain activity (7) and neurodegeneration (8). If confirmed, higher female AG might represent increased brain activity and even vulnerability to degeneration in women.

Finally, Goyal et al. (1) mention that their random forest algorithm could not accurately predict sex using said brain metabolic measures. This calls into question the extent of brain differences in this set of metabolic data.

Despite their controversial interpretation, this set of results suggests that fundamental differences exist between male and female metabolic brain rates, which deserve further investigation. Goyal et al. (1) should be praised for clearly identifying the issue of sex stratification in artificial intelligence (AI)-based brain research. The authors' data, in our view, demonstrate that algorithms trained on one sex are not necessarily predictive for the other sex, calling for sex-specific training of machine learning models. Sex-specific AI-based solutions will allow for greater accuracy of results for both men and women and should be implemented in basic and clinical research.

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