

RESEARCH ARTICLE

Men and women show partly distinct effects of physical activity on brain integrity

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Abstract

Introduction: Physical inactivity and female sex are independently associated with increased Alzheimer's disease (AD) lifetime risk. This study investigates the possible interactions between sex and physical activity on neuroimaging biomarkers.

Methods: In 134 cognitively unimpaired older adults (≥ 65 years, 82 women) from the Age-Well randomized controlled trial (baseline data), we investigated the association between physical activity and multimodal neuroimaging (gray matter volume, glucose metabolism, perfusion, and amyloid burden), and how sex modulates these associations.

Results: The anterior cingulate cortex volume was independently associated with sex and physical activity. Sex and physical activity interacted on perfusion and amyloid deposition in medial parietal regions, such that physical activity was related to perfusion only in women, and to amyloid burden only in men.

Discussion: Physical activity has both sex-dependent and sex-independent associations with brain integrity. Our findings highlight partly distinct reserve mechanisms in men and women, which might in turn influence their risk of AD.

KEYWORDS

aging, Alzheimer's, exercise, gender, multimodal neuroimaging, physical activity, reserve, sex

Highlights:

- Sex and physical activity have been linked to Alzheimer's disease (AD) progression.
- The association of sex and physical activity with brain health is partly independent.
- Different reserve mechanisms exist in men and women.

1 | INTRODUCTION

Alzheimer's disease (AD) pathogenesis is a complex phenomenon, characterized by a variety of cerebral changes at the molecular, functional, and structural levels, progressing over several decades and, eventu-

ally, leading to cognitive decline and dementia. Its progression appears to be influenced by the complex combination of modifiable and non-modifiable risk factors. Among those, female sex has long been incriminated due to a higher prevalence of AD dementia in women.¹ Although this fact is being questioned (² for review), it is now acknowledged

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that men and women present differences in their susceptibility to the disease and its progression.² Yet, the drivers of sex differences in AD remain to be fully understood and several factors are currently under investigation. For instance, the biological underliers of these sex effects have been evaluated and suggest a role for sexual hormones, including the effect of menopause/andropause and hormonal replacement therapies^{(3,4, for reviews), and sex chromosomes.⁵}

Beyond biological differences, increasing evidence highlights the importance of modifiable factors in dementia risk, including cardiovascular risk, lifestyle behavior, and psychoaffective factors.^{6,7} This association between environmental factors and dementia risk aligns with the concept of reserve,⁸ which relates healthier and enriched lifetime experiences with the accumulation of cerebral and cognitive capacities, allowing individuals to better resist to age- or disease-related alterations (resistance) and/or better cope with these alterations (resilience).⁹ Among these modifiable environmental factors, a large body of evidence links physical inactivity to increased dementia risk.^{10,11} Neuroimaging studies further indicate that physical activity in cognitively normal older individuals is associated with better neuroimaging outcomes, including hippocampal volume, amyloid burden, or tau pathology,^{12–18} even if some negative results exist (19 for review).

This link between environmental factors and dementia risk might explain part of the sex differences in susceptibility to AD. Indeed, social role and lifestyle behaviors differ between men and women, which refers to the concept of gender, and this might be associated with distinct levels of lifestyle-associated AD risk. In addition, the effect of environmental risk factors themselves could differ by sex, as the mechanisms by which risk factors influence the progression of pathology might differ between men and women. Notably, a previous meta-analysis suggests sex-specific effects of physical activity on cognitive outcomes, with potentially greater effect of physical activity on cognition in women.²⁰ However, little is known about the cerebral substrate of these sex-specific effects of physical activity, as only a few studies investigated the interactive effects of sex and physical activity on brain volume and the results are not fully consistent.^{21–23}

The objective of this study was to better understand the interplay between sex and physical activity on complementary markers of brain integrity in cognitively unimpaired older adults, focusing mainly on regions likely to be influenced by AD and reserve mechanisms.

2 | METHODS

2.1 | Participants

A total of 135 cognitively unimpaired participants (mean age \pm SD of 68.49 ± 3.26 ; 83 women) were included in the Age-Well randomized control trial (²⁴; see Flow Chart in Supplementary Material, eFigure S1). Age-Well aims at investigating the impact of meditation training on mental health and well-being in the aging population. After the baseline visit, participants were randomly assigned to an 18-month meditation-based intervention, 18-month foreign language learning intervention,

RESEARCH IN CONTEXT

1. Systematic Review: The authors reviewed the literature using traditional sources (eg, PubMed). The importance of studying sex/gender differences in the field of Alzheimer's disease (AD) research has been increasingly recognized. On the other hand, increasing evidence links physical activity and AD risk. However, the interplay between sex and physical activity on the brain remains poorly understood.
2. Interpretation: Our findings suggest the existence of both independent and interactive effects of sex and physical activity on makers of brain integrity in cognitively unimpaired older adults. These findings are consistent with the increasing acknowledgment of sex-specific mechanisms in AD progression.
3. Future Directions: These results are important for the understanding of AD progression and have major implications for clinical trials design by supporting the development of sex-specific therapeutical trials and the sex stratification for trials' monitoring and evaluation. Future studies will be needed to further understand the drivers of these sex-specific mechanisms.

or 18-month without intervention.²⁴ Only baseline data, prior to randomization, was analyzed in the present study. Here, "sex" stands for biological sex, as reported by the participant at inclusion. All participants were French native speakers age 65 or older. They all underwent at least 7 years of formal schooling, were selected based on the absence of psychiatric or neurological disease, and had normal cognition. Cognitive integrity was determined after neuropsychological evaluation and clinicians' consensus. Participants underwent extended clinical and behavioral evaluations, including questionnaires to assess lifestyle habits, blood testing, and multimodal neuroimaging.

The Age-Well randomized control trial, sponsored by Inserm, received approval from regional ethics committee (Comité de Protection des Personnes Nord-Ouest III, Caen, France; trial registration number: EudraCT: 2016–002441-36; IDRCB: 2016-A01767–44; ClinicalTrials.gov Identifier: NCT02977819) and all participants provided signed informed consent prior to participation.

2.2 | Physical activity questionnaire

Physical activity was assessed through the French version²⁵ of the Modifiable Activity Questionnaire(MAQ)²⁶. Participants were asked to list all leisure physical activities (eg, running, dance) they had participated in more than 10 times over the last 12 months. For each of these, participants were asked to specify how many times they did the activity (ie, how many months over the last year, how many weeks per month,

TABLE 1 Demographics

| | All | Women | Men | P * |
|---|---------------------|---------------------|---------------------|------|
| N (%) | 134 | 82 (61%) | 52 (39%) | |
| Age, years (\pm SD) | 69.33 (\pm 3.80) | 69.37 (\pm 3.74) | 69.27 (\pm 3.93) | .89 |
| Education, years (\pm SD) | 13.14 (\pm 3.09) | 12.52 (\pm 2.95) | 14.12 (\pm 3.09) | .004 |
| APOE ϵ 4 carriers, n (%) | 36 (26.87%) | 18 (22%) | 18 (34.6%) | .11 |
| MMSE score (\pm SD) | 29.04 (\pm 1.04) | 29.07 (\pm 1.03) | 28.98 (\pm 1.06) | .62 |
| Physical activity, hours per week (\pm SD) | 6.31 (\pm 4.91) | 6.33 (\pm 4.89) | 6.28 (\pm 4.97) | .96 |

*P-values of the differences between women and men were obtained from t-tests for continuous variables and chi-square test for fixed variables. Abbreviations: SD, standard deviation; APOE, apolipoprotein E gene; MMSE, Mini-Mental State Exam.

how many times per week) and the average duration of the activity per time, which enabled the calculation of the average hours per week. The average hours of physical activity practice per week over the last year was calculated by the sum of each activity's duration. Although imperfect (ie, subjective), such an index provides an estimation of habitual physical activity over the last year, more likely to be associated with markers of brain integrity that cannot show immediate changes (ie, non-functional measures) than other classic measurements over the last week or so. One participant (ie, one woman) had missing data, leading to a sample size of 134 participants for this study (Table 1).

2.3 | Neuroimaging acquisition

All participants were scanned on the same scanners at the Cyceron center (Caen, France).

A T1-weighted image and a fluid-attenuated inversion recovery (FLAIR) were acquired on a Philips Achieva 3T scanner in all participants ($n = 134$).

Fluorodeoxyglucose positron emission tomography (FDG-PET) and florbetapir-PET were obtained on two separate days on a Discovery RX VCT 64 PET-CT scanner (General Electric Healthcare). FDG-PET scans were acquired on a subset of 92 individuals (59 women), while florbetapir-PET was obtained in all but one participant ($n = 133$). A dual-phase florbetapir-PET scan was performed, including a first 10-minute scan starting at the time of injection (early florbetapir-PET), used to measure brain perfusion, and a second 10-minute scan starting 50 minutes after the injection (late florbetapir-PET), used to quantify amyloid burden. Early Florbetapir-PET scan was missing in one additional participant due to a scanner issue, such that early Florbetapir-PET was available for 132 participants. Final sample size per imaging modality is provided in the Flow Chart (eFigure 1, Supplementary Material). Details on acquisition parameters and procedures for magnetic resonance imaging (MRI) and PET images can be found elsewhere²⁴ and in the Supplementary Material (eMethods).

2.4 | Images processing

T1-weighted MRI was processed using the Segment routine of the Statistical Parametric Mapping software version 12 (SPM12, Wellcome

Trust Centre for Neuroimaging, London, UK; <http://www.fil.ion.ucl.ac.uk>), implemented in MATLAB (MathWorks, Natick, MA). Briefly, T1-weighted images were segmented using FLAIR images, normalized to the Montreal Neurological Institute (MNI) template, and modulated to account for the effects of spatial normalization. Modulation has the effect of preserving the total amount of gray matter signal in the normalized image, providing a measure corrected for individual brain sizes.

Each PET image was first registered to the corresponding T1-weighted MRI, and then normalized to the MNI template applying the parameters obtained from the Segment procedure (see above). The resulting images were then scaled by the average binding in the cerebellar cortex to obtain the standardized uptake value ratio (SUVR).

For each modality (MRI, FDG, and early and late florbetapir-PET), we extracted the average signal in two regions of interest (ROIs), constructed from the AAL atlas²⁷: (1) the anterior cingulate cortex (ACC) and (2) the precuneus and posterior cingulate cortex (PCC) (see Supplementary Material, eFigure 2). These regions were chosen as they have been shown to be involved in reserve/resilience and affected early in the course of AD.²⁸⁻³⁰

2.5 | Statistical analyses

Statistical analyses were conducted with SPSS Statistics (version 27).

Characteristics of men and women were compared using two-sample t-test (for continuous variables) or chi-square tests (for categorical variables). Association between covariates were explored using bivariate Spearman correlations.

The association between sex and the level of physical activity reported was assessed using two-sample t-test.

We used general linear models (GLMs) to assess, for each ROI and modality, (1) the effect of sex and physical activity and (2) the interaction between sex and physical activity. These analyses were conducted controlling for age, education, and APOE ϵ 4 status.

Effects were considered statistically significant at $P \leq .05$, uncorrected for multiple comparisons. Only effects at $P \leq .002$ would survive Bonferroni correction. Considering the exploratory nature of this study, a less-stringent approach was applied to assess the robustness of the results by applying a bootstrapping procedure (1000 iterations) on models showing significant ($P \leq .05$) or "close-to-significant" ($P \leq .10$) results.

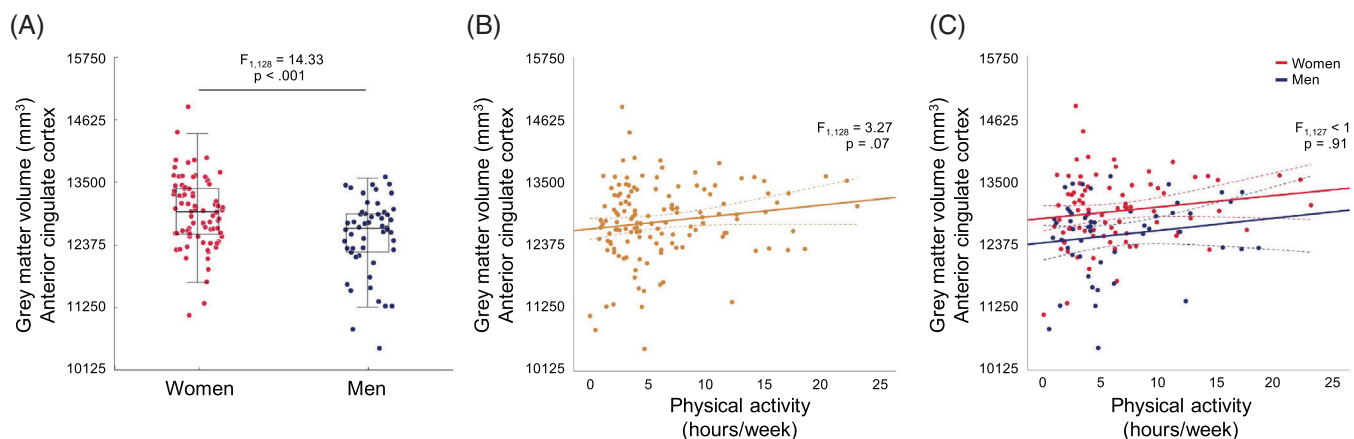


FIGURE 1 Independent effects of sex and physical activity on the anterior cingulate cortex volume. Effect of sex (A), physical activity (B), and their interaction (C) on the anterior cingulate cortex volume. Statistics for the effect of sex (A), physical activity (B), and the sex x physical activity interaction (C) were obtained from general linear models, controlling for age, years of education, and apolipoprotein E (APOE) $\epsilon 4$ status. Raw values are plotted. For (A), the interquartile range (25th percentile, median, and 75th percentile), the whiskers (lines indicating variability outside the upper and lower quartiles minimum value) and the individual dots are presented. For (B) and (C), dotted lines represent confidence intervals (95%)

Complementary analyses were conducted to assess the influence of different types of physical activity on the results. Therefore, GLMs were replicated using as predictor the average hours per week of each activity type, separately.

3 | RESULTS

3.1 | Participants' characteristics

A total of 134 cognitively unimpaired older adults were eligible for the analysis (Table 1; see Flow Chart - Supplementary material eFigure 1 for the sample size per imaging modality). The 82 women did not differ from the 52 men in terms of age, proportion of APOE $\epsilon 4$ carriers, or global functioning, as measured with the Mini-Mental State Examination (MMSE).³¹ However, men had a higher duration of formal schooling when compared to women. Bivariate correlations between the different variables included in this study are provided in the Supplementary Material (eFigure 3).

3.2 | Association between sex and physical activity

Women and men from this cohort did not differ regarding the average duration of physical activity that they reported engaging in over the last 12 months ($t_{132} = .05$, $P = .96$; Supplementary Material eFigure 4).

3.3 | Association between sex and neuroimaging

Sex was associated with differences in gray matter volume in the ACC, with women showing higher volume than men ($F_{1,128} = 14.33$, $P < .001$; Figure 1A). This effect remained significant after bootstrapping ($B = -453.84$; $P = .002$; 95% confidence interval [CI] -697.281 ,

-227.789). There were no sex effects (Table 2) on the other imaging modalities and ROIs.

3.4 | Association between physical activity and neuroimaging

ACC volume was non-significantly associated with the MAQ ($F_{1,128} = 3.27$, $P = .07$; Figure 1B), such that higher levels of physical activity seemed to be associated with higher gray matter volume in this region. Higher level of physical activity was also associated with greater glucose metabolism in the ACC ($F_{1,86} = 5.50$, $P = .02$; Figure 2A) and precuneus/PCC ($F_{1,86} = 6.04$, $P = .02$; Figure 2B). All effects were significant after bootstrapping ($B = 20.70$; $P = .05$; 95% CI .921, 41.735 for the association between MAQ and ACC volume; $B = .004$, $P = .04$; 95% CI $-.0001$, .007 and $B = .005$, $P = .03$; 95% CI .001, .008 for the association with glucose metabolism in the ACC and precuneus/PCC, respectively). The other measures were not associated with physical activity (Table 2).

3.5 | Interactions between sex and physical activity

An interaction between sex and physical activity was found for perfusion in the precuneus/PCC ($F_{1,125} = 3.86$, $P = .05$; Figure 3A). A non-significant sex x physical activity interaction on amyloid burden can be observed in the precuneus/PCC ($F_{1,125} = 3.68$, $P = .06$; Figure 3B). The bootstrap procedure suggests that the interaction on perfusion was not robust ($B = -.004$; $P = .06$; 95% CI $-.008$, .0003), whereas the one on amyloid was ($B = -.013$; $P = .05$; 95% CI $-.027$, .0006). The interaction of sex and physical activity on the precuneus/PCC perfusion was such that perfusion seemed to increase as a function of physical activity in women, whereas it was not the case in men (see Figure 3A). On the other hand, the interaction on the precuneus/PCC amyloid

TABLE 2 Association between sex, physical activity, and their interaction on multimodal neuroimaging

| | | Sex ^a | Physical activity ^b | Sex * Physical activity ^c |
|--------------------|---------------|-------------------------------------|---------------------------------|--------------------------------------|
| Gray matter volume | ACC | $F_{1,128} = 14.33$ $P < .001^*$ | $F_{1,128} = 3.27$ $P = .07$ | $F_{1,127} < 1$ $P = .91$ |
| | Precuneus/PCC | $F_{1,128} = 2.35$ $P = .13$ | $F_{1,128} = 1.59$ $P = .21$ | $F_{1,127} < 1$ $P = .36$ |
| Glucose metabolism | ACC | $F_{1,86} < 1$ $P = .73$ | $F_{1,86} = 5.50$ $P = .02$ | $F_{1,85} < 1$ $P = .38$ |
| | Precuneus/PCC | $F_{1,86} < 1$ $P = .77$ | $F_{1,86} = 6.04$ $P = .02$ | $F_{1,85} < 1$ $P = .71$ |
| Brain perfusion | ACC | $F_{1,126} = 2.05$ $P = .15$ | $F_{1,126} = 1.75$ $P = .19$ | $F_{1,125} < 1$ $P = .85$ |
| | Precuneus/PCC | $F_{1,126} < 1$ $P = .65$ | $F_{1,126} < 1$ $P = .74$ | $F_{1,125} = 3.86$ $P = .05$ |
| Amyloid burden | ACC | $F_{1,127} < 1$ $P = .88$ | $F_{1,127} < 1$ $P = .38$ | $F_{1,126} = 1.29$ $P = .26$ |
| | Precuneus/PCC | $F_{1,127} < 1$ $P = .53$ | $F_{1,127} = 1.68$ $P = .20$ | $F_{1,125} = 3.68$ $P = .06$ |

Abbreviations: ACC, anterior cingulate cortex; PCC, posterior cingulate cortex.

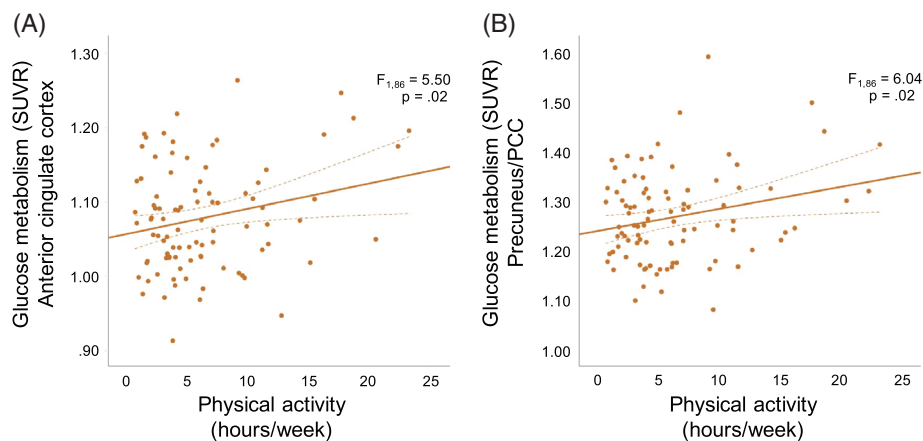
Results are considered significant at $P \leq .05$ and considered as a trend at $P \leq .10$.

^aStatistical values were obtained from general linear models controlling for age, years of education, apolipoprotein E (APOE) $\epsilon 4$ status, and physical activity.

^bStatistical values were obtained from general linear models controlling for age, years of education, apolipoprotein E (APOE) $\epsilon 4$ status, and sex.

^cStatistical values were obtained from general linear models controlling for age, years of education, apolipoprotein E (APOE) $\epsilon 4$ status, sex, and physical activity.

* Results significant after Bonferroni correction for multiple comparison.

**FIGURE 2** The specific effect of physical activity on glucose metabolism in the anterior cingulate cortex (A) and the precuneus/PCC (B).

Statistics were obtained from general linear models, controlling for age, sex, years of education, and apolipoprotein E (APOE) $\epsilon 4$ status. Raw values are plotted. Dotted lines represent confidence intervals (95%). Abbreviation: PCC, posterior cingulate cortex

burden revealed a negative association between amyloid load and physical activity in men, whereas no association appeared in women (see Figure 3B). No interactions were found on the other ROIs or modalities (Table 2).

3.6 | Complementary analyses

To better understand the influence of different types of activity on our results, analyses were stratified per activity type. Of note, no sex dif-

ferences were found when evaluating the average duration of physical activity for each specific activity type (Supplementary Material eFigure 5), or when classifying physical activity into aerobic vs resistance training (Supplementary Material eFigure 6; see Supplementary Material, eResults, for details). Because very few individuals reported resistance training, no additional analyses could be conducted but, when restricting the analyses to aerobic exercise, association between sex, physical activity, and brain integrity remained similar to those obtained with the total MAQ (see Supplementary Material, eResults, for details).

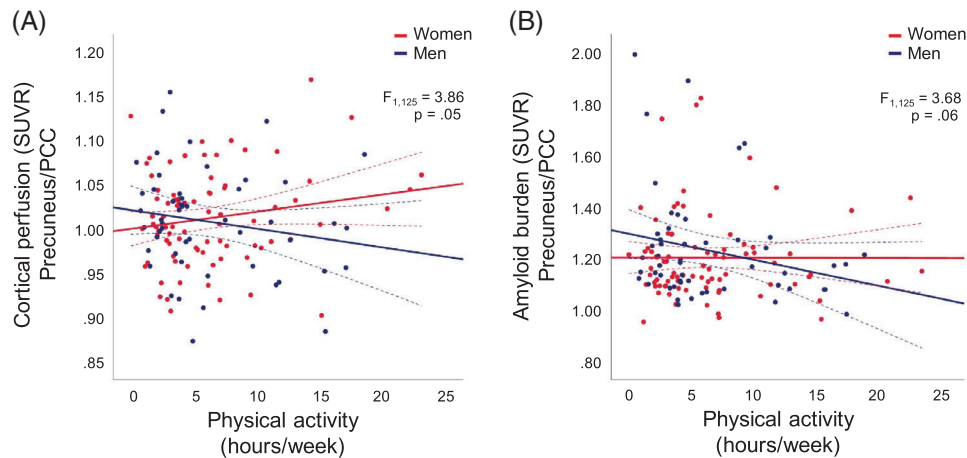


FIGURE 3 Interactive effects of physical activity and sex on the precuneus/PCC perfusion (A) and amyloid burden (B). Statistics for the sex x physical activity interactions were obtained from general linear models on the total sample, controlling for age, years of education, and apolipoprotein E (APOE) $\epsilon 4$ status, and including the main effects of sex and physical activity. Raw values are plotted. Dotted lines represent confidence intervals (95%). Abbreviation: PCC, posterior cingulate cortex; SUVR, standardized uptake value ratio

4 | DISCUSSION

Although we found no differences in the amount of reported leisure time physical activity between men and women, we reported both independent and interactive effects of sex and physical activity on markers of brain integrity in cognitively unimpaired older men and women. More specifically, gray matter volume in the ACC was associated with sex, with a greater volume in women when compared to men, and physical activity, with higher levels of physical activity being associated with greater volume. However, there was no interaction between sex and physical activity on this region. On the other hand, glucose metabolism was specifically associated with physical activity, with no effect of sex or interaction between sex and physical activity on this measure. Finally, we evidenced interactive effects of sex and physical activity in the precuneus/PCC, suggesting that higher levels of physical activity were associated with greater cortical perfusion in women, whereas it was associated with reduced amyloid burden in men. Although the bootstrapping method suggests that these results are robust, most results would not survive correction for multiple comparison ($P \leq .002$ for Bonferroni correction). As a result, interpretations of these findings should be taken with caution.

In this study, the effect of sex was limited to gray matter volume, with higher ACC volume in women. This finding is consistent with that of previous studies indicating that, although head size is larger in men, cognitively unimpaired older women show higher gray matter volume and cortical thickness when compared to men, including in the ACC.³²⁻³⁴ In the literature, the effect of sex on other markers of brain integrity is less robust. Although studies on glucose metabolism are sparse but tend to indicate greater glucose metabolism in older women when compared to older men,^{35,36} previous studies on amyloid burden failed to identify differences between men and women.³⁷⁻⁴⁰ Of importance, this absence of sex differences in amyloid or other markers of brain integrity does not necessarily imply the absence of sex differences in the downstream effects of such brain alterations.^{37,41}

In addition to being associated with sex, the ACC volume seemed to be associated with physical activity (significant only after bootstrapping). This result is interesting considering that the ACC has been linked previously to reserve and/or reserve proxies.^{15,28,42} It is notably consistent with previous findings linking greater metabolism in frontal medial regions and female sex on the one hand, and markers of reserve and resilience on the other hand.^{28,36} These studies advocated that the greater preservation of the ACC in cognitively unimpaired older women could underly higher resilience in women and support the female advantage usually found for cognition.⁴³ Of importance, the effects of sex and physical activity highlighted here were obtained while controlling each factor for the other, and in the absence of interaction between them. Therefore, it suggests that the greater resilience found in women and at a higher level of physical activity, as evidenced by greater volume of the ACC in the present study, is, at least partly, independent.

We also found a specific association between glucose metabolism and physical activity, with no association with sex. This finding also supports the existence of sex-independent effects of physical activity on the brain. Inconsistent findings have been reported in the literature with regard to the effects of physical activity in general, including on glucose metabolism¹⁹ for review,⁴⁴. This might reflect the fact that effects are subtle and could also be due to the large variability in physical activity measurements among studies, that vary from self-report to objective or physical measures, covering variable periods of time and considering a wide range of activities.

Of interest, in addition to these independent effects of sex and physical activity, we highlighted interactive effects of sex and physical activity on brain perfusion and amyloid burden. These interactions were identified in parietal medial regions (precuneus/PCC), which suggests potentially important clinical implications considering that the precuneus/PCC is referred to as a hub, particularly sensitive to aging and AD.³⁰ It is notably thought to be one of the most sensitive region to early amyloid accumulation⁴⁵ and its function is altered in AD,³⁰ with

complementary evidence for early perfusion alterations in preclinical AD.⁴⁶

To the best of our knowledge, only a few studies investigated the interplay between sex and physical activity on neuroimaging, and they focused on brain volume measures but not on perfusion or amyloid deposition. They found differential effects of physical activity in men and women but diverged in the direction of these differences. Thus, although the effect of physical activity was only found in women in two studies, on the prefrontal cortex and on the hippocampus, respectively,^{21,23} the reversed pattern was found with evidence of a positive association with hippocampal and parahippocampal volumes only in men^{21,22}; respectively. However, these studies greatly differed in their samples' characteristics, including the existence of sex differences in the level of physical activity or not, but also the metrics used to assess physical activity (ie, subjective vs objective, evaluated for the last days vs over years) are likely to explain the discrepancy in their results.

The interactive effects of sex and physical activity highlighted here add to these results, suggesting the existence of a sex-specific association between physical activity and brain integrity that goes beyond brain structure. Because no sex differences were found in the amount of physical activity reported here, we interpret these effects as the result of sex-specific mechanisms rather than sex-specific lifestyle risk profiles. The greater association between physical activity and perfusion in women aligns with previous evidence pointing toward a greater effect of physical activity on cognitive performance in women.²⁰ More particularly, the increased perfusion associated with a higher physical activity could support compensation mechanisms in women (eg, increased perfusion might support greater network function and sustain cognition), as previously suggested using different methodologies or reserve proxies.^{28,36} On the other hand, a higher level of physical activity in men could act through different mechanisms involving resistance to amyloid accumulation (eg, increased amyloid clearance⁴⁷). This differential association between physical activity and brain integrity in men vs women suggests the existence of partly distinct reserve mechanisms according to biological sex. Although the exact underliers of this remains to be tested, previous works suggest the implication of sex-specific immune mechanisms,²² sex hormones,⁴⁸ sex differences in neuroplasticity, dopaminergic, or cardiovascular activity⁴⁹ for review), by which physical activity might differently promote brain and cognitive health in men and women. Of note, although we found no differences in the average amount of physical activity reported by men and women, or when investigating more specifically the type of activity, we cannot rule out the possibility that the specific components and intensity of exercise differ between sexes. Therefore, it is still possible that other differences in the characteristics of the activities have different health benefits in men and women.⁵⁰ Future studies should more directly assess the mechanisms underlying the sex-specific influence of physical activity and further evaluate the specificity of each type of physical activity (type and intensity) on brain health in men and women.

This study has several limitations, including a relatively small sample size (particularly when considering FDG-PET data) and the use of phys-

ical activity questionnaire (ie, subjective and imprecise report) instead of an objective measurement of physical activity. Nevertheless, the questionnaire used in the present study provides information on physical activity over a long period (ie, over the last 12 months), which we believe has the advantage of allowing a more accurate approximation of habitual physical activity when compared to measurements considering only the last week and, therefore, strongly rely on the characteristics of this specific week. Complementary analyses suggest that results are driven mainly by aerobic exercise, but we were not able to fully characterize the influence of different types of physical activities and their components, notably taking into account the intensity or social components of exercise. In addition, we selected only two brain regions a priori, based on their association with reserve and AD. By choosing these regions a priori, we were able to provide information on the effect of sex and physical activity on markers relevant for brain health, but we cannot exclude the presence of additional associations in other brain regions. We must also acknowledge that the effects are overall subtle, with no correction for multiple comparisons. Therefore, all interpretations should be taken with caution and results will require replication. Finally, due to the cross-sectional design of this study, no causality could be inferred.

Overall, our study demonstrates the existence of both sex-dependent and sex-independent associations between physical activity and brain health in older individuals. This suggests that the mechanisms underlying reserve partly differ between men and women, even if more studies are needed to better understand the drivers of these sex-dependent mechanisms. These results were found in regions that are sensitive to reserve/resilience and AD and add to the growing literature advocating for a better acknowledgement of sex differences both for the study of AD pathophysiology and the development and evaluation of clinical trials.

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CONFLICTS OF INTERESTS

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SUPPORTING INFORMATION

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APPENDIX

Collaborators–Medit-Ageing Research Group

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| Martine Batchelor | Bordeaux, France | Independent meditation teacher |
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| Axel Beaugonin | Caen, France | Independent meditation teacher |
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| Thien (Titi) Huong Tran (Dolma) | Lyon, France | Meditation teacher |
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