A Report on "Randomized Controlled Trial of Resistance Exercise and Brain Aging Clocks" by Gonzalez-Gomez et al. (2026)

Reviewer 2

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> I am wiser than this person; for it is likely that neither of us knows anything fine and good, but he thinks he knows something when he does not know it, whereas I, just as I do not know, do not think I know, either. I seem, then, to be wiser than him in this small way, at least: that what I do not know, I do not think I know, either.
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> Plato, *The Apology of Socrates*, 21d

> To err is human. All human knowledge is fallible and therefore uncertain. It follows that we must distinguish sharply between truth and certainty. That to err is human means not only that we must constantly struggle against error, but also that, even when we have taken the greatest care, we cannot be completely certain that we have not made a mistake.
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> Karl Popper, 'Knowledge and the Shaping of Reality'

Overview

Citation: Gonzalez-Gomez, R., Demnitz, N., Coronel, C., Gates, A. T., Kjaer, M., Siebner, H. R., Boraxbekk, C.-J., & Ibanez, A. M. (2026). Randomized Controlled Trial of Resistance Exercise and Brain Aging Clocks. *GeroScience*

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Abstract Summary: This study investigates the impact of resistance training on brain health by quantifying its effect on brain aging using longitudinal assessments. It utilizes resting-state functional magnetic resonance imaging (rs-fMRI) data from 2,433 healthy adults to train models that predict brain age, which are then applied to 309 participants from a randomized trial.

Key Methodology: Randomized controlled trial (Live Active Successful Aging - LISA trial) with 309 participants assigned to heavy-resistance training, moderate-intensity training, or a non-exercise control group. Longitudinal assessments using resting-state functional magnetic resonance imaging (rs-fMRI) at baseline, 1, and 2 years. Brain clock models trained on an independent dataset of 2,433 healthy adults were used to estimate brain age gaps.

Research Question: What is the effect of resistance training on brain aging and functional connectivity in older adults?

Summary

Is It Credible?

Gonzalez-Gomez et al. present a randomized controlled trial investigating whether one year of resistance training can slow brain aging in older adults. Using resting-state functional magnetic resonance imaging and machine learning models, the authors claim that both heavy and moderate resistance training significantly reduce a person's estimated brain age compared to a non-exercise control group (p. 2). They further assert that these benefits are driven by global, distributed network changes rather than localized effects, and that the improvements last up to a year after the supervised intervention ends (pp. 6, 9). The study also links these neurological changes to physical performance, noting an association between improved leg strength and a reduced brain age gap.

While the randomized design is a strength, the headline claim that the physical act of resistance training directly decelerates brain aging is complicated by the choice of control group. The intervention groups received supervised training sessions, regular social interaction, and a structured routine, whereas the non-exercise group simply maintained their habitual lifestyle with only periodic follow-up calls (p. 3). Without an active control group matched for social contact and routine, it is difficult to determine whether the observed reductions in brain age stem from the physiological exertion of lifting weights or the well-documented cognitive benefits of psychosocial engagement. The authors acknowledge that associations with muscle strength were relatively small and inconsistent, suggesting other behavioral mediators might be at play, but the structural confound of the control group remains a significant limitation (p. 9).

The study's reliance on the brain age gap as a direct proxy for biological brain health also introduces uncertainty. The brain clock model was trained on cross-sectional

data from over 2,400 individuals to predict chronological age (p. 1). Applying this model to track within-person longitudinal change assumes that the neurological differences between people of different ages perfectly mirror the changes a single brain undergoes over time. The authors attempt to validate this longitudinal application by correlating changes in the brain age gap with improvements in leg strength, but the resulting association is remarkably weak, explaining just 1.4 percent of the variance in the full sample (p. 6). While they do report that intra-group variability outweighed inter-group differences as a check on reliability, this does not fully validate the biological meaning of the longitudinal change (Supplementary Material 5).

Furthermore, the narrative reconciling the study's various findings is somewhat disjointed. The authors conclude that resistance training has a global impact on brain aging because network-specific brain clocks failed to show significant differences, which relies on a null finding that may simply reflect lower statistical power in those sub-models (p. 8). Conversely, their voxel-level analysis highlights highly localized increases in prefrontal connectivity exclusively in the heavy training group (p. 5). Finally, the claim that the intervention has lasting effects is based on brain age measurements taken a year after the supervised program ended (p. 9). Although physical performance (leg strength) was measured at this follow-up, the study does not present detailed activity logs confirming whether participants continued to exercise independently during this second year. Thus, it is difficult to know if the sustained benefits represent a permanent neurological shift or simply the result of ongoing, unmonitored physical activity. Ultimately, the study provides intriguing preliminary evidence that structured resistance training programs are associated with more favorable brain aging trajectories, but the specific claims of causal, lasting, and global biological deceleration are somewhat overstated given the methodological limits.

The Bottom Line

Gonzalez-Gomez et al. offer an interesting application of machine learning to neuroimaging, suggesting that resistance training can reduce a person's estimated brain age. However, the study's reliance on a non-exercise control group makes it difficult to separate the physiological effects of exercise from the cognitive benefits of social interaction and a structured routine. Additionally, using a cross-sectional model to track longitudinal changes in brain health introduces significant methodological uncertainty. While the findings support the general benefits of staying active, the specific claim that resistance training durably decelerates biological brain aging requires more rigorous validation.

Potential Issues

Lack of an active control group introduces a significant psychosocial confound: The study's design, which compares two active exercise interventions to a non-exercise control group, cannot fully disentangle the physiological effects of resistance training from the psychosocial benefits of participating in a structured program. Participants in the intervention groups received supervised sessions, social interaction with trainers and peers, a routine, and expert attention. While the control group received regular follow-up calls, they lacked the intensive social and structural components of the intervention arms (p. 3). These psychosocial factors are known to influence cognitive and brain health. Without an active control group—for example, a group participating in a social club or stretching sessions matched for time and social contact—it is difficult to rule out the alternative explanation that the observed benefits in brain age are due to these non-exercise-related factors.

The study relies on "Brain Age Gap" as a proxy for brain health without sufficient internal validation: The article treats a statistical construct, the Brain Age Gap (BAG), as a direct "index of brain health status" and claims that exercise "decelerates brain ageing" (p. 2). BAG is the residual error from a model predicting chronological age. While the authors cite external literature to support this construct, the study provides very little internal evidence to validate it within the trial sample. The only internal validation regarding biological relevance was a correlation between BAG changes and changes in leg strength, which was found to be very weak ($r = -0.12$ for the full sample) and inconsistent across groups, being significant only in the moderate-intensity group (p. 6). Without demonstrating a stronger link between the BAG measure and relevant clinical or cognitive outcomes in its own participants, the study's interpretation of a change in the model's output as a meaningful change in biological "brain health" remains a significant interpretive leap.

The validity of using a cross-sectional brain clock for longitudinal change is a central assumption: The study's core measurement tool, the "brain clock," was trained on cross-sectional data from 2,433 individuals of different ages (p. 1). It was then used to measure within-person change over a two-year period. This approach relies on the assumption that the differences between people of different ages at one point in time are equivalent to the changes that occur within a single person as they age. This assumption is often not valid, as the brain characteristics that distinguish a 65-year-old from a 67-year-old in a population snapshot may not be the same characteristics that change within one person's brain over two years. While the authors note that intra-group variability outweighed inter-group differences, this statistical check does not confirm that the model is accurately capturing the *biological* process of aging within individuals (Supplementary Material 5).

Claims of "lasting effects" are potentially confounded by unmonitored post-intervention behavior: The article concludes that resistance training has "lasting effects beyond the training period" because benefits to the Brain Age Gap were still present at the 2-year follow-up, one year after the supervised intervention ended (p. 9). While the study did measure physical performance at year 2, it does not present detailed activity logs to confirm the extent of independent exercise during this period (p. 3). It is therefore difficult to determine whether the observed effects persisted due to a lasting physiological change induced by the initial one-year intervention, or because participants in the exercise groups simply continued to train on their own while the control group remained sedentary.

Contradictory findings on the mechanisms of brain change are reconciled with a speculative narrative: The study's different analyses produce a disjointed picture of the intervention's effects. The brain clock analysis found that both heavy (HRT) and moderate (MIT) training produced a similar, significant, and globally distributed reduction in brain age (p. 6). In contrast, the voxel-level analysis found a localized increase in prefrontal connectivity only in the HRT group, with no effect in the MIT

group (p. 5). Furthermore, a correlation between strength gains and brain age reduction was found only in the MIT group, not the HRT group (p. 6). The article attempts to reconcile these disparate findings by proposing a "hierarchical organization" where global changes are "expressed through regional focal patterns" (p. 7). This appears to be a post-hoc narrative developed to reconcile the observed results rather than a pre-specified, testable hypothesis.

The statistical evidence linking physical strength to brain age is fragile: The study's primary evidence for a mechanistic link between physical and brain health is a weak Spearman correlation of $r = -0.12$ ($p = 0.036$) between changes in leg strength and changes in BAG for the full sample (p. 6). This association explains only 1.4% of the variance. The authors then report that this correlation was only statistically significant in the moderate-intensity training (MIT) subgroup ($r = -0.21$, $p = 0.038$). While the figure caption implies FDR correction was used, a p-value so close to the threshold in a subgroup analysis remains fragile evidence upon which to build a narrative about "expected group dynamics" (pp. 7–8).

The conclusion of a "global" brain effect is weakly supported and potentially overstated: The article argues that the effects of exercise on brain aging are global and distributed, rather than localized to specific networks. This conclusion is based on the fact that the whole-brain clock model showed an effect while network-specific brain clock models "did not yield any statistically significant effects" (p. 6). Relying on a null finding to support a conclusion is logically weak, as the network-specific models may simply have been underpowered, a possibility supported by their poorer performance metrics (Supplementary Table 2, p. 17). Furthermore, concluding that exercise has a "global" effect on "brain aging" is a strong claim based on a single imaging modality (resting-state fMRI).

Reporting of longitudinal data could be more complete: The study collected data at baseline, 1 year, and 2 years. While the primary outcome (BAG) is reported for both follow-ups, key mechanistic analyses are only reported for the 1-year follow-up

(Table 4, p. 8). Specifically, the voxel-level analysis of functional connectivity was conducted only for the "baseline to the 1-year follow-up" period (p. 4). By omitting the 2-year results for this mechanistic analysis, the article misses an opportunity to provide a full assessment of whether the proposed mechanisms (e.g., increased prefrontal connectivity) also persisted alongside the primary outcome.

Minor transparency and reporting issues: Several details that would aid in the assessment of the study are not fully elaborated. First, the article lacks quantitative data on intervention adherence, such as the percentage of sessions completed, which is important for interpreting the dose-response relationship; it does, however, reference the primary trial publications where this information is likely available (p. 3). Second, the control group was "instructed to maintain their habitual physical activity levels," but the article does not report data confirming their compliance (p. 3). Third, the number of participants included in the longitudinal analyses fluctuates between the 1-year and 2-year time points, but the article does not explicitly state this, which could lead to misinterpretation of the numbers as cumulative dropout (Table 4, p. 8). Finally, Table 1 reports the "Years of education" for the non-exercise group as having a mean of 14.6 and a standard deviation of 7.9, with a range of 9.5 to 17 (p. 3). A standard deviation of 7.9 is mathematically impossible for a variable with a range of 7.5 years, indicating a typographical error.

Future Research

Active control designs: Future studies should employ active control groups that match the intervention arms in social contact, attention, and routine. For instance, a control group participating in supervised stretching or a social club would help isolate the specific neurobiological effects of physical exertion from the psychosocial benefits of participating in a structured trial.

Longitudinal biomarker validation: To confidently use brain clocks as measures of intervention efficacy, future work must validate these models on longitudinal datasets. Training algorithms to predict within-person trajectories rather than cross-sectional age differences would provide a much more accurate tool for assessing whether a lifestyle intervention genuinely alters the pace of biological aging.

Comprehensive behavioral tracking: Claims regarding the lasting effects of an intervention require rigorous monitoring of participant behavior during follow-up periods. Future trials should utilize wearable fitness trackers and detailed activity logs to account for ongoing exercise habits after the formal intervention concludes, ensuring that sustained neurological benefits are accurately attributed to the original program rather than continued independent training.

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