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# Abstract

**Background and objectives:** Functional outcomes after stroke are strongly related to focal injury measures. However, the role of global brain health is less clear. Here, we examined the impact of brain age, a measure of neurobiological aging derived from whole brain structural neuroimaging, on post-stroke outcomes, with a focus on sensorimotor performance. We hypothesized that more lesion damage would result in older brain age, which would in turn be associated with poorer outcomes. Related, we expected that brain age would mediate the relationship between lesion damage and outcomes. Finally, we hypothesized that structural brain resilience, which we define in the context of stroke as younger brain age given matched lesion damage, would differentiate people with good versus poor outcomes.

**Methods:** We conducted a cross-sectional observational study using a multi-site dataset of 3D brain structural MRIs and clinical measures from ENIGMA Stroke Recovery. Brain age was calculated from 77 neuroanatomical features using a ridge regression model trained and validated on 4,314 healthy controls. We performed a three-step mediation analysis with robust mixed-effects linear regression models to examine relationships between brain age, lesion damage, and stroke outcomes. We used propensity score matching and logistic regression to examine whether brain resilience predicts good versus poor outcomes in patients with matched lesion damage.

**Results:** We examined 963 patients across 38 cohorts. Greater lesion damage was associated with older brain age ( $\beta=0.21$ ; 95% CI 0.04,0.38,  $P=0.015$ ), which in turn was associated with poorer outcomes, both in the sensorimotor domain ( $\beta=-0.28$ ; 95% CI: -0.41,-0.15,  $P<0.001$ ) and across multiple domains of function ( $\beta=-0.14$ ; 95% CI: -0.22,-0.06,  $P<0.001$ ). Brain age mediated 15% of the impact of lesion damage on sensorimotor performance (95% CI: 3%,58%,  $P=0.01$ ). Greater brain resilience explained why people have better outcomes, given matched lesion damage (OR=1.04, 95% CI: 1.01,1.08,  $P=0.004$ ).

**Conclusions:** We provide evidence that younger brain age is associated with superior post-stroke outcomes and modifies the impact of focal damage. The inclusion of imaging-based assessments of brain age and brain resilience may improve the prediction of post-stroke outcomes compared to focal injury measures alone, opening new possibilities for potential therapeutic targets.

## Introduction

A critical topic in stroke research is understanding why some patients demonstrate better outcomes than others, despite similar amounts of lesion damage. To address this question, research has traditionally focused on two spatial levels of brain injury: the focal level (i.e., the lesion and how it injures individual brain structures, such as the corticospinal tract<sup>1-4</sup>) and the network level (i.e., how brain structures that are functionally or structurally connected to the lesioned area but distant from the injury are nonetheless affected, e.g., via diaschisis<sup>5-7</sup>). However, a third level has also recently begun to garner attention in stroke research: *global brain health*, which represents the cellular, vascular, and structural integrity of the entire brain. The integrity of residual brain tissue may be critical for neural plasticity following stroke.<sup>8,9</sup> Acute stroke studies show that early measures of poor brain health, such as atrophy, markers of white matter disease, and prior infarcts throughout the brain, are associated with poorer outcomes on the modified Rankin scale and cognition at 90 days,<sup>10</sup> while better structural integrity is associated with better modified Rankin scores.<sup>11</sup> However, little attention has been given to the role of global brain health in *chronic* stroke or in relation to domain-specific rehabilitation outcomes,<sup>12</sup> such as sensorimotor impairment.

Here, we specifically focused on a measure of global brain health known as *brain age*, a neurobiological construct derived from whole brain structural neuroimaging.<sup>13,14</sup> To calculate brain age, a machine learning algorithm is trained to associate chronological age with neuroimaging-based indices of interest (e.g., patterns of whole brain structural integrity from regional thickness, surface area, and volumes). The trained model is then used to predict brain age in new individuals. A higher brain predicted age difference (*brain-PAD*), calculated as the difference between a person's predicted brain age minus their chronological age, suggests that the brain appears to be older than the person's chronological age. An older-appearing brain has been associated with different disease states, including Alzheimer's disease,<sup>15</sup> major depression,<sup>16</sup> and traumatic brain injury,<sup>17</sup> as well as with increased risk of mortality<sup>14</sup> and more severe disease progression<sup>18,19</sup> However, brain age has not been widely explored in stroke. Two studies have demonstrated that brain-PAD is higher after stroke compared to healthy controls<sup>20</sup> and reliable across time.<sup>21</sup> However, no associations have been reported between brain age and either infarct volume or post-stroke sensorimotor outcomes.



Beyond *brain age*, we also examine the concept of structural *brain resilience*, which we define in the context of stroke as the maintenance of structural whole brain integrity, measured as younger brain age, despite matched lesion damage. This concept draws upon research on cognitive resilience in “super-agers,” or older adults who demonstrate exceptional cognitive performance despite their advanced age.<sup>22</sup> These individuals are thought to demonstrate biological resilience to traditional aging pathways (e.g., identified through neuroimaging, genetic, or histologic profiles) compared to their peers.<sup>22,23</sup> However, while cognitive resilience refers to maintained *behavioral* performance despite common age-related neurological changes, here we aimed to study maintained *brain structural integrity* despite matched focal injury. We suggest that greater brain resilience to focal lesion damage should result in younger-appearing brains, while less brain resilience should make the brain more vulnerable to widespread degeneration after the same amount of injury and manifest as older-appearing brains, with subsequent changes in behavior.

Using subsets of the data, we tested the following four hypotheses: First, we hypothesized that more lesion damage and longer time since stroke should be related to higher brain-PAD, which may reflect loss of structural integrity due to post-stroke secondary atrophy. Second, we hypothesized that higher brain-PAD would be associated with worse sensorimotor outcomes, as well as worse global outcomes across multiple functional domains, due to less residual brain tissue available to support neuroplastic changes required for recovery. We anticipated that this relationship would be strongest in the ipsilesional hemisphere, which should undergo more changes with functional relevance compared to the contralesional hemisphere, and in chronic stroke, allowing for time after stroke for secondary atrophy to occur.<sup>24-26</sup> Third, we hypothesized that brain-PAD would mediate the impact of known focal injury measures, such as corticospinal tract lesion load (CST-LL),<sup>1-3</sup> on sensorimotor outcomes, and that this relationship would again be strongest in the ipsilesional hemisphere in chronic stroke. Finally, we hypothesized that greater brain resilience despite stroke-related injury would distinguish people with better versus worse sensorimotor outcomes. That is, given the same amount of focal brain damage, we expected people with less global brain damage, as indexed by lower brain-PAD, to have better outcomes than people with more global brain damage.

# Methods

## Study design and patients

Cross-sectional, multi-site data were pooled from the ENIGMA Stroke Recovery Working Group, and frozen for this analysis on January 24, 2022. A full description of the data and procedures used by the ENIGMA Stroke Recovery Working Group has been reported elsewhere (see also eMethods in the Supplement).<sup>24,27</sup> Briefly, stroke neuroimaging and behavioral data from retrospective studies are contained in a repository, which is queried to extract data meeting study-specific eligibility criteria. For the current study, we extracted data that had: (1) FreeSurfer outputs from 3D T1-weighted structural brain MRI volumes (see *MRI Data Analysis*), (2) a sensorimotor behavioral outcome measure (see *Behavioral Data*), (3) covariates of age and sex, and (4) a primary stroke reported in either cerebral hemisphere. Some analyses used subsets of this data with specific characteristics (e.g., early stroke ( $\leq 6$  weeks post-stroke) versus chronic stroke ( $\geq 180$  days post-stroke), or manually segmented lesion masks to extract focal injury metrics (see *Lesion Analysis*). See eMethods and eFigure 1 for more information about subanalyses.

## Standard Protocol Approvals, Registrations, and Patient Consents

All data were collected in accordance with the Declaration of Helsinki and in compliance with local ethics boards at each respective institute. Written informed consent was obtained from all participants in the study. Approval was received from the University of Southern California Health Science Campus Institutional Review Board (IRB# 00002881) to conduct the current study.

## MRI Data Analysis

### Brain Age Analysis

As previously detailed,<sup>24,27</sup> MRI data from each cohort were visually inspected upon receipt for quality control and again after each processing step. The brain imaging software FreeSurfer (version 5.3) was used to automatically segment the T1-weighted MRIs. Subsequently 153 features of interest were extracted: 68 measures of cortical thickness, 68 measures of cortical surface area, 14 measures of subcortical volume, 2 lateral ventricle volumes, and the total intracranial volume (ICV). Left and right hemisphere features were then averaged, resulting in a total of 77 features of interest.

We calculated predicted brain age using a model published by Han et al., which is a ridge regression model trained on a cohort of 4,314 healthy controls between 18-75 years old.<sup>16</sup> Although there are many excellent methods for defining brain age, we specifically selected this model as it was developed on multi-site retrospective data collected from 19 cohorts from different countries, similar to our multi-site dataset. In addition, this model is publicly available, allowing for greater scientific reproducibility ([https://www.photon-ai.com/enigma\\_brainage](https://www.photon-ai.com/enigma_brainage)). The model requires tabular data from FreeSurfer outputs (i.e., the 77 features of interest described above), rather than raw image data. Following Han et al.,<sup>16</sup> we estimated brain age using separate models for males and females. We then calculated brain-PAD by subtracting chronological age from predicted brain age:

$$\text{brainPAD} = \text{Predicted Brain Age} - \text{Chronological Age}$$

Brain age was derived from the mean of both hemispheres for all analyses, except for ipsilesional versus contralesional brain age analyses, which were derived from only ipsilesional or only contralesional brain measures. As lesioned tissue could have impacted brain age estimation, we also include lesion volume and corticospinal tract lesion load in the models to account for the possible confounding effect of lesion damage on brain age (see *eMethods* in the Supplement for more information on quality control and model performance metrics).

### **Lesion Analyses**

In a subset of the data for which we received raw T1-weighted MRIs and could identify observable lesions, lesion masks were manually segmented by trained research team members based on a previously published lesion segmentation protocol.<sup>28,29</sup> Lesions were preprocessed with intensity non-uniformity correction, intensity standardization, and registration to the MNI-152 template, as detailed previously.<sup>29</sup> Lesion volume (measured in voxels) and percent of CST-LL, or overlap, were calculated using the open-source Pipeline for Analyzing Lesions after Stroke toolbox.<sup>30</sup> We used a publicly available CST template that includes origins from both primary and higher order sensorimotor regions,<sup>31</sup> which was found to be more strongly associated with post-stroke sensorimotor impairment than a CST template derived from primary motor cortex alone.<sup>1</sup>

## Behavioral Data Analysis

We harmonized different behavioral measures collected across cohorts by defining a primary *sensorimotor outcome score*, which was the percentage of the maximum possible score each individual achieved, as done previously<sup>24</sup> (*eMethods in the Supplement*). This resulted in a score where 100 indicated no impairment and 0 indicated severe impairment. We also examined a single measure of sensorimotor impairment (FMA-UE), as well a single measure of global stroke severity across several domains (e.g., sensorimotor, language, and cognitive deficits; NIHSS; *eMethods*),<sup>32</sup> in subsets of the data with these specific measures. Given the associations of brain-PAD with many different clinical disease states, we expected brain-PAD to be related to all functional outcome measures.

## Statistical Analysis

We used a one-way ANOVA to examine differences between the standard brain age prediction calculated from the mean of both hemispheres, from the ipsilesional hemisphere only, and from the contralesional hemisphere only. We used robust linear mixed-effects regression models to examine associations between brain-PAD, sensorimotor outcomes, and lesion damage. Full methodological details can be found in the *eMethods in the Supplement*.

We performed a mediation analysis using a three-step segmentation approach.<sup>33,34</sup> In this analysis, we examined: (1) the effect of the independent variable (lesion damage) on the mediator (brain-PAD), (2) the effect of the mediator (brain-PAD) on sensorimotor outcomes, and (3) the mediation effects of brain-PAD on the relationship between lesion damage and sensorimotor outcome.

In the first step, we tested whether CST-LL influenced brain-PAD. We included covariates of lesion volume, age, sex, ICV, and days post stroke as fixed effects and cohort as a random effect.

In the second step, we examined whether brain-PAD impacted sensorimotor impairment, with covariates of age, sex, and ICV and a random effect of cohort. We also examined if this relationship was maintained when looking specifically at sensorimotor impairment in a subset of participants with the FMA-UE and in a subset with a multi-domain measure (NIHSS; *eMethods in the Supplement*). We further hypothesized that if this brain-behavior relationship is reflective of post-stroke atrophy, it should be strongest in the ipsilesional hemisphere in chronic stroke. We therefore examined ipsilesional versus contralesional brain-PAD separately, and at two different times post-stroke as in our previous work<sup>24</sup> (early stroke ( $\leq 6$

weeks post-stroke, thought to represent the premorbid brain prior to secondary degeneration)<sup>20</sup> and chronic stroke ( $\geq 180$  days post-stroke)).

In the last step, we performed a mediation analysis to examine whether brain-PAD mediates the impact of CST-LL on sensorimotor outcomes. We tested the significance of the indirect effect using bootstrapping procedures. Unstandardized indirect effects were computed for 5,000 bootstrapped samples, and the 95% confidence interval was computed by determining the indirect effects at the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles (*eMethods* in the Supplement). As part of the mediation analysis, we replicated the previously-shown relationship between CST-LL and sensorimotor outcomes.<sup>1-3</sup> To further explore the relationship between brain-PAD and CST-LL, we also performed a supplemental regression analysis to test whether there is an interaction between these two factors on sensorimotor outcomes (*eMethods*).

Finally, we examined whether structural brain resilience explains why some people have better versus worse outcomes, despite the same amount of lesion damage. We operationally defined *structural brain resilience* as lower brain-PAD (younger brain age) despite equal amounts of lesion damage (both CST-LL and lesion volume), which we expected to be associated with better outcomes. We used logistic regression to test whether brain-PAD could distinguish those with better versus worse outcomes, after matching for extent of focal lesion damage between groups. As previously published guidelines for the FMA-UE established cut-offs for mild versus severe impairment at above 42 and below 27 points, respectively (corresponding to sensorimotor scores of 63.6% and 40.9%).<sup>35</sup> As our dataset is comprised of the FMA-UE along with other sensorimotor measures, we adapted this guideline by dividing the data into the top and bottom thirds (roughly corresponding to the FMA-UE cut-offs) to represent good versus poor outcomes, respectively. We matched the groups on both lesion damage to the corticospinal tract (CST-LL) and extent of lesion damage (lesion volume), using 1:1 nearest neighbor propensity score matching without replacement and a stringent caliper of 0.05 standard deviations of the propensity score.<sup>36</sup> We estimated propensity score using logistic regression of the outcome on the covariates of CST-LL and lesion volume. We then used logistic regression on the matched dataset to predict better versus worse outcomes as a binary variable, with brain-PAD as the primary predictor and covariates of age, sex, ICV, and cohort.

All statistical analyses were run in R (version 3.6.3; R Core Team, 2020);<sup>37</sup> see the *eMethods* in the Supplement for the full list of libraries. For all analyses, we present beta coefficients

( $\beta$ ) for predictors, along with the sample size (n), *t*-value, standard error (SE), degrees of freedom (df), 95% confidence interval (CI), and *p*-value in tables.

## Data availability

The brain age model<sup>16</sup> can be freely accessed from: [https://www.photon-ai.com/enigma\\_brainage](https://www.photon-ai.com/enigma_brainage), and code for extracting FreeSurfer features of interest and formatting them for brain age analyses can be from: <https://github.com/npl/ENIGMA-Wrapper-Scripts>. The CST region of interest atlas<sup>31</sup> can be freely accessed from: <http://lrnlab.org/>. Our T1w MRI data and accompanying lesion masks are publicly available here:<sup>29</sup> [http://fcon\\_1000.projects.nitrc.org/indi/retro/atlas.html](http://fcon_1000.projects.nitrc.org/indi/retro/atlas.html). Additional summary data and code from this study are available upon reasonable request from the corresponding author (see *eMethods* in the Supplement).

## Results

As of January 24, 2022, the ENIGMA Stroke Recovery Working Group<sup>27</sup> dataset contained data from 1,221 patients. Cross-sectional data from 963 individuals with stroke from 38 cohorts across 10 countries met the current eligibility criteria and were included in this analysis (Table 1; eTable 1 in the Supplement). There were 607 males and 356 females, with a median age of 61 years (interquartile range (IQR):16 years). Stroke severity (i.e., primary sensorimotor score) ranged from 0-100 (median:78.46, IQR:49.78). Chronicity ranged from 1-7,439 days (median:244 days, IQR:875 days; ). Data were collected early after stroke ( $\leq 6$  weeks) in 205 participants and in the chronic stage ( $\geq 180$  days) in 558 participants. Lesion volume ranged from 0.013-294.80 mL (median:6.38 mL, IQR:3.47 mL). A probabilistic lesion overlap map can be found in eFigure 2.

Older predicted brain age was positively associated with older chronological age and larger ventricle volumes and was negatively correlated with smaller regional cortical thickness, cortical surface area, and subcortical volume measures (Figure 1; eResults in the Supplement). Ipsilesional brain-PAD was significantly higher than brain-PAD calculated from the mean of both hemispheres, while contralesional brain-PAD was significantly lower ( $F(2,2802) = 53.69, P < 0.001$ ).

## **1. Higher brain-PAD occurs with more lesion damage and longer time after stroke**

In the first step of our three-step mediation analysis, we examined the effect of the independent variable (lesion damage) on the mediator (brain-PAD). We tested our first hypothesis that brain-PAD is larger when there is more lesion damage and longer time since stroke. Using a subset of data with lesion metrics and days since stroke ( $n=639$ ), we found that both CST-LL ( $\beta=0.21$ ,  $P=0.015$ ) and lesion volume ( $\beta=2.83$ ,  $P<0.001$ ) were positively associated with brain-PAD, such that more CST-LL and larger lesions resulted in higher brain-PAD (eTable 2 in the Supplement). Longer time post-stroke (e.g., more chronic stroke) was significantly associated with higher brain-PAD ( $\beta=1.14$ ,  $P=0.026$ ). Age was negatively correlated with brain-PAD ( $\beta=-0.53$ ,  $P<0.001$ ), such that younger adults showed higher brain-PAD. This was anticipated due to a known regression dilution effect,<sup>38</sup> in which younger samples are predicted to be older and older samples are predicted to be younger due to a regression towards the mean; this is a key reason why chronological age is included as a covariate (see *eMethods*).

## **2. Poorer sensorimotor outcomes are associated with higher brain-PAD**

In the second step of our mediation analysis, we examined whether the mediator (brain-PAD) influences the dependent variable (post-stroke outcomes), testing our second hypothesis that higher brain-PAD would be associated with worse outcomes. Across the entire cohort ( $n=963$ ), higher brain-PAD was associated with worse sensorimotor outcomes ( $\beta=-0.28$ ,  $P<0.001$ ; Table 2). There was also an association with sex ( $\beta=3.40$ ,  $P=0.028$ ), with females demonstrating worse sensorimotor behavior than males. The brain age relationship was also maintained when examining a specific measure of sensorimotor impairment (FMA-UE;  $n=528$ ;  $\beta=-0.30$ ,  $P=0.004$ ) and a multi-domain measure of stroke severity (NIHSS;  $n=238$ ,  $\beta=-0.14$ ,  $P<0.001$ ; eTable 3 in the Supplement).

We then tested our hypothesis that the impact of brain-PAD on sensorimotor outcomes is driven by post-stroke secondary atrophy, in which case, we expected to see the strongest associations in the ipsilesional hemisphere in chronic stroke. Indeed, larger ipsilesional brain-PAD was negatively associated with worse sensorimotor outcome ( $\beta=-0.30$ ,  $P<0.001$ ; Table 2). This relationship was maintained when adding total lesion volume and CST-LL into the model ( $\beta=-0.17$ ,  $P=0.008$ ), suggesting these effects are independent of direct lesion damage (eTable 4 in the Supplement). There was no detectable association with contralesional brain-

PAD ( $\beta=-0.05$ ,  $P=0.436$ ; eTable 5). We also found a significant relationship between worse sensorimotor behavior and larger brain-PAD in chronic stroke ( $n=558$ ;  $\beta=-0.26$ ,  $P=0.002$ ; Table 2), but not in early stroke ( $n=205$ ;  $\beta=-0.13$ ,  $P=0.386$ ; eTable 6).

### **3. Brain-PAD mediates the impact of lesion damage on post-stroke outcomes**

In the third step of our mediation analysis, we tested our hypothesis that the relationship between the independent variable (CST-LL) on the dependent variable (post-stroke outcomes) is mediated by brain-PAD. We examined this in a subset of the sample with lesion measures ( $n=674$ ; see eMethods, eResults, eDiscussion and eTables 7–12 in the Supplement), as well as in the ipsilesional hemisphere of patients with chronic stroke only ( $n=437$ ), expecting strongest results in ipsilesional, chronic stroke in line with our results above. In the whole sample, there was a marginally significant effect of brain-PAD mediating the impact of CST-LL on sensorimotor outcomes (Figure 2), with indirect effects of  $-0.045$  ( $P=0.068$ ; 95% CI from  $-0.11$  to  $0.00$ ). The proportion of the effect of CST-LL on sensorimotor outcome that goes through the mediator (brain-PAD) was  $0.04$  ( $P=0.068$ ; 95% CI from  $-0.004$  to  $0.12$ ). However, as expected, when only examining ipsilesional brain-PAD in chronic stroke (Figure 2), the mediation effect of brain-PAD was significantly stronger, Brain-PAD mediated the impact of CST-LL on chronic sensorimotor outcomes (Figure 2), with indirect effects of  $-0.11$  ( $P=0.007$ ; 95% CI from  $-0.24$  to  $-0.02$ ). The proportion of the effect of CST-LL on sensorimotor outcome that goes through the mediator (brain-PAD) was  $0.15$  ( $P=0.01$ ; 95% CI from  $0.03$  to  $0.58$ ). In a supplementary analysis, we also show an interaction between CST-LL and brain-PAD, in which brain-PAD has the largest impacts on outcomes when there is little to no CST-LL ( $n=748$ ;  $\beta=0.02$ ,  $P=0.05$ ; eTable 13).

### **4. Structural brain resilience dissociates good versus poor outcomes in people with matched focal lesion damage**

For any given amount of lesion damage, we found that brain-PAD was highly variable (IQR: 16.16 years; range:  $-28.48$  to  $36.08$  years). We therefore tested our fourth hypothesis that greater structural brain resilience, measured as younger brain age despite matched lesion damage, explains why some people have good versus poor outcomes. Propensity score matching was applied to participants with good ( $n=249$ ) versus poor ( $n=250$ ) sensorimotor outcomes on both lesion volume and CST-LL, resulting in a final matched sample of 244 participants (122 matched samples; 255 unmatched samples were discarded from subsequent



analysis). The matching was successful, as evidenced by no difference in either CST-LL or lesion volumes between groups after matching (eTable 14 in the Supplement).

Using logistic regression, we found that brain-PAD significantly dissociated people with good versus poor outcomes (brain-PAD: OR=1.04, 95% CI from 1.01 to 1.08,  $P=0.004$ ; Table 3), such that people with poor outcomes had higher brain-PAD than people with good outcomes, despite matched CST-LL and lesion volume (brain-PAD:  $-3.07 \pm 10.3$  years versus  $2.52 \pm 11.3$  years in better versus worse groups, respectively; Figure 3), even after controlling for age, sex, ICV, and site. Similar results were found when examining only people with chronic stroke using ipsilesional brain-PAD (OR=1.05, 95% CI from 1.02 to 1.08,  $P=0.002$ ; eTables 15–16 in the Supplement).

## Discussion

In this study, we demonstrate that larger brain age gap is associated with greater stroke damage and longer time after stroke, as well as with worse post-stroke functional outcomes. We also show that brain age mediates the relationship between lesion damage and sensorimotor outcomes. This is important because CST integrity has repeatedly been shown to be a robust biomarker of post-stroke sensorimotor performance and recovery, and these findings suggest that brain age and brain resilience may modify the impact of focal lesion damage on sensorimotor outcomes, underscoring the key role of neuroimaging markers of biological aging in stroke research.

### **Brain age gap is larger with greater stroke damage and longer time after stroke**

Stroke has a deleterious effect on the whole brain.<sup>39-42</sup> Here, we show that after unilateral stroke, older brain age is correlated with smaller cortical and subcortical measurements and larger ventricles, suggesting that brain age captures measures of whole-brain atrophy in stroke. Brain age predicted from the ipsilesional hemisphere was older than brain age predicted from the contralesional hemisphere, suggesting stronger effects in ipsilesional tissue. Larger brain age gap is associated with larger lesion extent, more damage to sensorimotor structures (CST-LL), and longer time after stroke (i.e., more chronic stroke). Altogether, these findings suggest that focal damage may worsen whole brain structural

integrity, with stronger effects over time, possibly representative of post-stroke secondary atrophy. However, it is unclear what the underlying effect of added brain aging is at different ages in patients with stroke (e.g., a 40-year-old versus a 70-year-old). Future studies should examine the effects of stroke on brain age longitudinally to test the hypothesis that stroke accelerates ipsilesional brain aging, with implications for both outcomes and treatment.

### **Older brain age is associated with worse post-stroke functional outcomes**

Our study also establishes significant behavioral associations between brain age and functional outcomes in people with stroke. We report associations between worse outcomes and older brain age, both for sensorimotor impairment specifically (FMA-UE) and for general stroke severity (NIHSS). These findings suggest that brain-PAD is a sensitive neuroimaging marker of brain health after stroke across multiple domains. Older brain age, possibly due to post-stroke atrophy, may reflect limited capacity for post-stroke brain repair and subsequent recovery. Structural loss reflected in older brain age may occur following stroke via multiple pathways, such as through vascular or glymphatic system dysfunction or widespread inflammation.<sup>43,44</sup> Associations between brain age and sensorimotor impairment were strongest in the ipsilesional hemisphere in chronic stroke, suggesting that the relationship is impacted by post-stroke atrophy. Brain age may be a valuable non-invasive biomarker that represents an amalgamation of neurodegenerative processes, likely accumulated both before and after stroke. Further research with longitudinal data and diverse measures of function are needed to examine whether and how brain age influences post-stroke recovery and, conversely, whether and how stroke accelerates brain aging.

### **Brain age mediates the impact of CST-LL on sensorimotor outcomes**

In the third step of our mediation analysis, we show that, when examined together with a known focal injury predictor (CST-LL), brain age additionally predicts outcomes, with a causal relationship, such that brain age mediates 15% of the effects of CST-LL on outcomes. This mediation effect is strongest in the ipsilesional hemisphere in chronic stroke, again suggestive of post-stroke atrophy. Specifically, we found that larger CST-LL is associated with older brain age, and the resulting older brain age further worsens outcomes beyond the effects of CST-LL alone. Overall, these results suggest that focal damage, plus subsequent global damage, have an additive effect on sensorimotor outcomes.

## **Brain resilience differentiates better versus worse outcomes, despite matched lesion damage**

Finally, we show that whole brain structural resilience to lesion damage differentiates people with good versus poor outcomes. Brain age itself was associated with lesion volume, such that larger lesions were associated with larger brain-PAD, but the lesion volume itself did not impact sensorimotor behavior. This suggests that what is important is how the rest of the brain reacts to the lesion (e.g., secondary damage, or conversely, subsequent plasticity) - more so than the amount of damage due to the infarct itself. In line with this, we found that brain age was highly variable across individuals with similar amounts of lesion damage (e.g., Figure 3). We therefore examined whether brain resilience to the lesion, which we defined as lower brain age despite similar amounts of lesion damage, would dissociate people with better versus worse sensorimotor outcomes. Using logistic regression, we found that people with younger brain age tend to be more resilient: their outcomes are better than expected. Contrarily, people with older brain age tend to be less resilient and thus more vulnerable: their outcomes are worse than expected for the same amount of injury. This supports our hypothesis that greater structural brain resilience - as indexed by smaller brain-PAD despite similar amounts of lesion damage - is a significant predictor of better sensorimotor outcomes. Altogether, these results suggest that it is not necessarily the amount of lesion damage at the time of stroke that solely determines sensorimotor outcomes, but also the susceptibility of the brain to widespread deterioration *after* the focal injury.

Although concepts such as brain age and brain resilience are being actively explored in other neurodegenerative fields of study and in acute stroke,<sup>11,22</sup> there has been limited extension of these concepts particularly to chronic stroke research and in relation to domain-specific rehabilitation outcomes<sup>12</sup> (e.g., Fugl-Meyer Assessment). Further research should examine whether brain age can provide a reliable indicator of the brain's readiness for repair by examining whether brain age can predict response to engaging in specific rehabilitation therapies.

### **Limitations and future directions**

Future work would benefit from large-scale longitudinal studies to measure the trajectory of brain aging during the weeks following a stroke to ascertain whether stroke accelerates brain aging. This is critical, as recent work suggests that cross-sectional brain age may reflect either early life differences or volume loss due to isolated incidents, such as stroke.<sup>45</sup> Furthermore,

as noted previously,<sup>24,25</sup> although our large, heterogeneous dataset provides statistical power and diverse data to test hypotheses, there are limited covariates that are present across the entire dataset. Additional factors known to influence brain age - such as genetics, neurodegenerative co-pathology such as microvascular damage, lifestyle factors, and comorbidities - should be examined in future studies. Additional harmonization of prospectively collected data across the acute and chronic stroke timeline, as recommended by the Stroke Recovery and Rehabilitation Roundtable,<sup>46,47</sup> would also allow for larger samples to explore questions more broadly and with greater power. In addition, while we show that lesion volume is related to older brain age, it is possible that larger lesions could bias brain age estimation. However, previous papers using similar FreeSurfer-based methods have demonstrated reliable brain age estimates in stroke,<sup>20,21</sup> and we employed several additional quality control steps to prevent skewed brain age estimations (see *eMethods* in the Supplement). Finally, as there is now active research examining treatments to prevent or slow brain aging (e.g., from aging and Alzheimer's disease research),<sup>48,49</sup> these interventions should be explored to assess whether they could improve functional outcomes after stroke.

<http://links.lww.com/WNL/C720>

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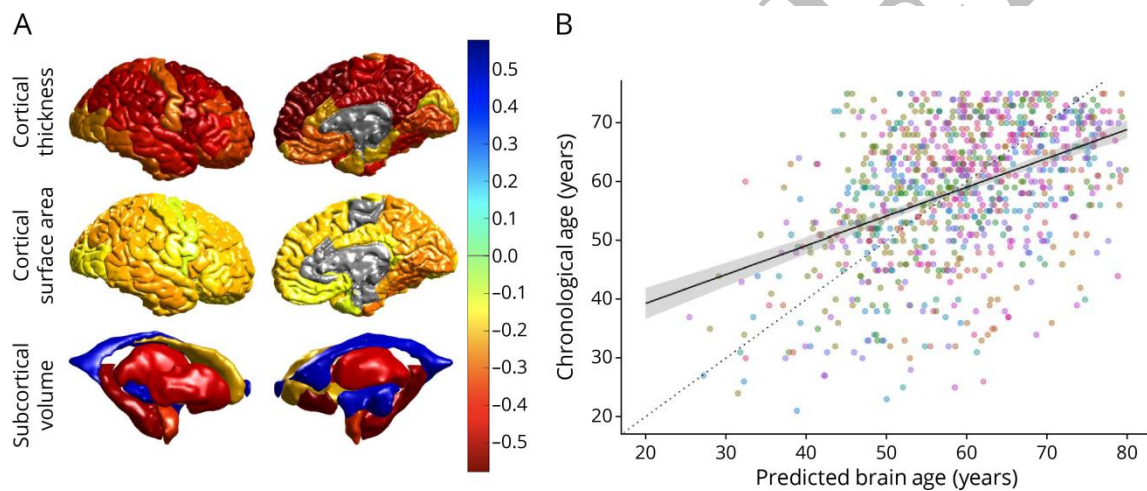
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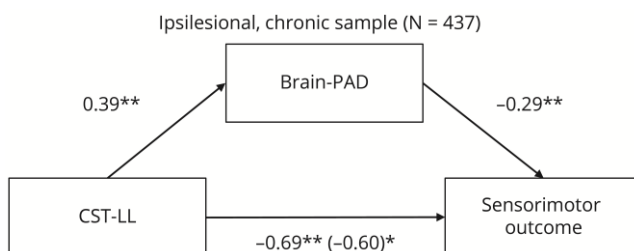
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## Figure Legends

**Figure 1 Brain age associations in people with stroke.** (A) Visualization of correlations between predicted brain age and region-of-interest measurements (top: cortical thickness, middle: cortical surface area, bottom: subcortical volumes). Warmer colors indicate stronger negative associations (e.g., larger volumes associated with younger predicted brain age), while cooler colors indicate stronger positive associations (e.g., larger ventricles associated with older predicted brain age). (B) Chronological age by predicted brain age across the entire sample. The identity line (dotted) and fixed effects model regression line (solid) are displayed with standard error in gray shading; different research cohorts are indicated by color.

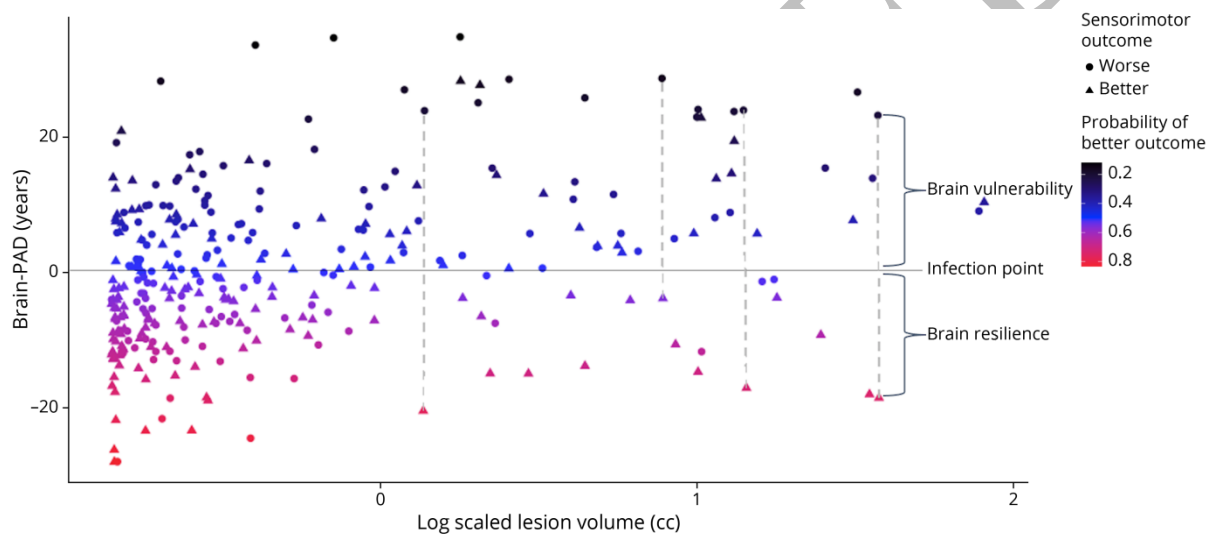


**Figure 2 Brain-PAD mediates the effects of CST-LL on sensorimotor outcome.** The effects of CST-LL on sensorimotor outcome, as mediated by brain-PAD, are depicted in the chronic stroke sample using ipsilesional brain-PAD. The mediated effect of CST-LL is shown in the bottom parenthesis. Significance values are denoted as follows: \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .





**Figure 3 Brain resilience dissociates sensorimotor outcome.** Visualization demonstrating that lower brain-PAD (shown on the y-axis) dissociates those with good (top third) versus poor (bottom third) sensorimotor outcomes (depicted by triangles and circles, respectively), when matched for lesion damage (n=244). The solid horizontal gray line is the point of inflection where the probability of having a better versus worse outcome is 0.5, with higher probability of better outcome depicted in warmer colors. The logarithm of scaled lesion volume (cc) is shown on the x-axis. Examples of matched pairs with similar lesion volumes, connected by the dotted vertical lines, are shown, with brain resilience shown in association with lower brain-PAD and brain vulnerability shown in association with higher brain-PAD.



## Tables

**Table 1 Summary of research cohort characteristics.** Age and sensorimotor score are shown as the median for each cohort, with the interquartile range (IQR) and range (minimum-maximum) shown in parentheses.

Cohort ID	Country	<i>n</i>	Age	Sex (F/M)	Median Sensorimotor Score
1	USA	34	60 (16, 31-75)	10 / 24	65.2 (23.5, 0-88)
2	USA	11	68 (13, 39-74)	5 / 6	53.0 (43.2, 20-73)
3	USA	12	58 (16, 33-71)	5 / 7	26.5 (30.3, 8-61)
4	Germany	17	44 (14, 30-68)	5 / 12	14.4 (16.7, 2-51)
5	USA	25	63 (12, 44-75)	11 / 14	81.8 (40.9, 21-100)
7	UK	38	56 (14, 18-75)	12 / 26	86.0 (31.6, 37-100)
8	USA	8	62 (10, 39-75)	2 / 6	55.0 (35.0, 0-100)
9	Norway	80	68 (17, 24-75)	26 / 54	100.0 (6.4, 57-100)
10	China	24	59 (13, 42-74)	5 / 19	100.0 (1.5, 68-100)
11	China	29	57 (11, 44-71)	10 / 19	100.0 (4.5, 9-100)
12	New	37	66 (18, 31-74)	18 / 19	66.7 (71.2, 3-97)
13	New	33	64 (19, 33-75)	12 / 21	21.2 (37.9, 3-97)
15	USA	14	57 (11, 45-74)	6 / 8	72.0 (24.6, 38-83)
17	USA	16	59 (4, 45-68)	5 / 11	54.5 (22.7, 23-74)
18	USA	11	59 (7, 46-73)	5 / 6	65.2 (22.0, 53-89)
19	Germany	13	62 (21, 33-74)	3 / 10	84.0 (8.0, 77-92)
20	Germany	18	64 (12, 49-75)	7 / 11	89.0 (8.8, 71-100)
21	Germany	8	62 (23, 40-75)	1 / 7	91.6 (13.1, 60-100)
22	Germany	17	59 (30, 25-72)	4 / 13	62.5 (50.0, 0-81)
23	USA	10	57 (10, 31-64)	6 / 4	38.6 (18.6, 27-79)
24	USA	18	62 (11, 32-72)	10 / 8	95.0 (0.0, 60-95)
25	Canada	22	60 (17, 37-75)	9 / 13	93.5 (39.8, 0-100)
27	USA	27	56 (9, 37-68)	7 / 20	28.2 (18.0, 0-57)
28	USA	26	62 (11, 23-75)	7 / 19	75.0 (24.6, 35-100)
31	USA	31	57 (9, 21-74)	8 / 23	51.5 (35.6, 20-91)
34	USA	14	58 (13, 32-65)	6 / 8	82.6 (21.2, 58-95)
35	Brazil	14	63 (18, 31-75)	6 / 8	70.5 (44.7, 15-94)
38	Italy	68	63 (20, 30-75)	27 / 41	92.5 (46.3, 0-100)
40	Italy	31	62 (20, 27-75)	16 / 15	65.0 (42.5, 10-100)
41	Australia	58	65 (10, 32-75)	23 / 35	100.0 (4.2, 83-100)
42	Brazil	29	48 (15, 25-75)	15 / 14	62.0 (20.0, 21-80)
46	USA	6	62 (6, 51-63)	1 / 5	43.9 (16.7, 27-91)
47	Australia	39	64 (10, 43-75)	12 / 27	65.2 (34.8, 6-98)
48	Canada	31	67 (14, 37-75)	12 / 19	75.8 (43.9, 0-100)
49	USA	8	62 (15, 37-71)	5 / 3	95.2 (1.2, 90-100)
52	USA	28	60 (14, 34-74)	11 / 17	43.2 (9.1, 21-52)
53	UK	48	61 (17, 26-75)	19 / 29	90.5 (19.6, 38-100)
54	USA	10	64 (10, 51-72)	4 / 6	40.2 (78.4, 3-100)

Abbreviations: F = females, M = males.

**Table 2 Relationship between post-stroke sensorimotor outcomes and brain-PAD.**

Summary statistics from robust mixed-effects linear regression to test associations between overall sensorimotor score and brain-PAD (left), brain-PAD derived only from the ipsilesional hemisphere (middle), and brain-PAD in chronic stroke only (right). Sex is coded as a factor (females=0, males=1). *ICV* stands for intracranial volume. The sample size (*n*), conditional  $R^2$ , beta coefficient (*beta*), standard error (*SE*), 95% confidence interval (*CI*), and *p-value* for all fixed effect covariates are reported. Significant predictors are denoted in bold.

<i>Predictors</i>	<b>WHOLE COHORT</b> N = 963, $R^2 = 0.596$				<b>IPSI LESIONAL BRAIN AGE</b> N = 950, $R^2 = 0.589$				<b>CHRONIC STROKE ONLY</b> N = 558, $R^2 = 0.592$			
	<i>beta</i>	<i>SE</i>	<i>CI</i>	<i>p-value</i>	<i>beta</i>	<i>SE</i>	<i>CI</i>	<i>p-value</i>	<i>beta</i>	<i>SE</i>	<i>CI</i>	<i>p-value</i>
Brain-PAD	<b>-0.28</b>	<b>0.07</b>	<b>-0.41 – -0.15</b>	<b>&lt;0.001</b>	<b>-0.30</b>	<b>0.05</b>	<b>-0.41 – -0.20</b>	<b>&lt;0.001</b>	<b>-0.26</b>	<b>0.09</b>	<b>-0.43 – -0.10</b>	<b>0.002</b>
Age	-0.05	0.06	-0.17 – 0.08	0.462	-0.07	0.06	-0.19 – 0.06	0.299	0.01	0.09	-0.16 – 0.19	0.886
Sex	<b>3.40</b>	<b>1.55</b>	<b>0.37 – 6.43</b>	<b>0.028</b>	2.93	1.55	-0.10 – 5.96	0.058	2.83	2.01	-1.11 – 6.77	0.159
ICV	-0.61	0.78	-2.14 – 0.92	0.437	-0.35	0.78	-1.88 – 1.17	0.651	-0.99	1.01	-2.98 – 1.00	0.330

**Table 3 Brain-PAD dissociates good versus poor sensorimotor outcomes.** Summary statistics from the logistic regression showing impact of brain resilience on outcomes. Good outcome is coded as 0, and poor outcome is coded as 1, such that higher (worse) brain-PAD is related to a higher likelihood of poor outcome. Sex is coded as a factor (females=0, males=1). *ICV* stands for intracranial volume. The sample size (*n*), conditional  $R^2$ , odds ratio, beta coefficient (*beta*), standard error (*SE*), 95% confidence interval (*CI*), and *p-value* for all fixed effect covariates are reported. Significant predictors are denoted in bold. Significant predictors are denoted in bold.

<b>SENSORIMOTOR OUTCOME (BINARY)</b>					
N = 244, $R^2 = 0.07$					
<i>Predictors</i>	<i>Odds Ratio</i>	<i>beta</i>	<i>SE</i>	<i>CI</i>	<i>p-value</i>
<b>Brain-PAD</b>	<b>1.04</b>	<b>0.04</b>	<b>0.01</b>	<b>1.01 – 1.08</b>	<b>0.004</b>
Age	0.99	-0.01	0.01	0.96 – 1.02	0.476
Sex	1.24	0.22	0.34	0.64 – 2.42	0.521
ICV	0.86	-0.15	0.17	0.62 – 1.19	0.377

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