Association of Epilepsy Surgery With Changes in Imaging Defined Brain Age

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Statistical Analysis performed by: Christophe de Bézenac, University of Liverpool, PhD

Search Terms: [ 66 ] Epilepsy surgery, [ 68 ] Hippocampal sclerosis, [ 120 ] MRI

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ABSTRACT

Objective: To determine whether surgery in patients with mesial temporal lobe epilepsy (mTLE) is associated with reduced brain-predicted age as a neural marker overall brain health, we compared brain-predicted and chronological age difference (Brain Age Gap Estimation: BrainAGE) in patients before and after surgery to healthy controls.

Methods: We acquired 3D T1-weighted MRI scans for 48 patients with mTLE before and after temporal lobe surgery to estimate brain-age using a gaussian processes regression model. We examined BrainAGE before and after surgery controlling for brain volume change, comparing patients to 37 age and sex matched controls.

Results: Preoperatively, patients showed an increased BrainAGE of more than seven years compared to controls. However, surgery was associated with a mean BrainAGE reduction of five years irrespective of whether or not surgery resulted in complete seizure freedom. We additionally observed a lateralisation effect as patients with left mTLE had BrainAGE values that more closely resembled control group values following surgery.

Conclusions: Our findings suggest that while morphological brain alterations linked to accelerated aging have been observed in mTLE, surgery may be associated with changes that reverse such alterations in some patients. This work highlights the advantages of resective surgery on overall brain health in patients with refractory focal epilepsy.

Key words: brain age; epilepsy; surgery; outcome; MRI
Introduction

Mesial temporal lobe epilepsy (mTLE) is one of the most common forms of focal epilepsy\(^1\) associated with a number of pathological alterations linked to premature brain aging.\(^2\) For one third of patients with mTLE anti-seizure medication is ineffective,\(^3\) leading to surgery program referrals that aim to localise and resect the epileptogenic zone.\(^4,5\) Between 27–67\% of patients who have surgery become completely seizure free.\(^6\)

Despite a risk of cognitive deterioration related to residual function in resected brain tissue, surgery can result in neuropsychological improvements,\(^7\) particularly when seizures are controlled and drug load reduced.\(^8\) The imaging literature provides evidence for post-operative brain network plasticity in support of restorative brain function.\(^9,10\) However, there is currently still no reliable biomarker to assess the effect of surgery on overall brain health.

A machine learning model for estimating chronological age from structural MRI scans has shown promise.\(^11,12\) Increased brain-predicted age (relative to actual age) indicates accelerated aging or higher cumulative exposure/sensitivity to pathological brain insults, in contrast to brain resiliance.\(^13\) The Brain-Age-Gap-Estimation (BrainAGE) has been used to examine neurodegenerative and psychiatric disorders and the influence of gene interaction, environment, and life burden.\(^14\) In epilepsy, increased BrainAGE was observed in patients with refractory focal epilepsy\(^15\) and patients with TLE and inter-ictal psychosis.\(^16\)

In this study we tested the effect of neurosurgery on BrainAGE as a measure of overall brain health, comparing 48 patients with mTLE before and after surgery to 37 controls. We expected patients to have higher BrainAGE but that successful surgery would be associated with an overall decrease.
Methods

Participants. We analysed the structural T1-weighted (T1w) MR images obtained from 48 patients (25 female) with refractory mTLE and neuroradiologically defined unilateral hippocampal sclerosis (HS) (mean age 39.08 years, SD 12.73) who underwent amygdalohippocampectomy at University Hospital Bonn, Germany. Patients (n = 48) were part of a consecutive series of patient (n = 115) being considered for surgery that enrolled into the study and had both pre- and post-operative T1w data suitable for analysis. After confident diagnosis of unilateral mTLE based on standard clinical protocols and detailed presurgical evaluation, patients underwent selective amygdalohippocampectomy in either the left (n=17) or right (n=31) hemisphere, with subtemporal (n= 21) or transsylvian (n=27) access. Presurgical evaluation included interictal electroencephalography (EEG) with video monitoring and, where clinically required, additional intracranial electrode recording, MRI scanning, and neuropsychological testing. HS diagnosis was made by a neuroradiologist experienced in epilepsy lesion detection on the basis of hippocampal volume loss and structural alterations observed on the MRI scans. HS was histologically confirmed in all resected specimens. Follow-up structural T1-weighted scans were acquired for all patients after surgery (mean 1.56 years, SD 0.99, between surgery and the follow-up scan; mean 1.96 years, SD 0.92, between first and second scans). The International League Against Epilepsy (ILAE) outcome classification system was used for postoperative seizure outcome follow up: 26 were rendered seizure/aura free (SF) (ILAE I) while 22 patients continued to have seizures (PS) (ILAE II-VI) following surgery. Clinical data for patient outcome groups is outlined and compared in Table 1. We also analysed MR images from a sample of 37 neurotypical controls similar in age and sex to the individuals who underwent surgery for epilepsy (mean age 40.08 years, SD 13.94; 21 females).

Magnetic resonance imaging. All participants were scanned on a 3 Tesla scanner (Magnetom Trio, Siemens, Erlangen, Germany) and an eight-channel head coil at the Life &
Brain Center in Bonn. Three-dimensional T1-weighted MPRAGE images were used for the BrainAGE analysis (160 slices, repetition time (TR) = 51300 ms, inversion time (TI) = 5650 ms, echo time (TE) = 53.97 ms, resolution 1.0 x 1.0 x 1.0 mm$^3$, flip angle 10 degrees).

**Brain age prediction.** Brain-predicted age was computed from raw T1-weighted MRI scans using the brainAgeR analysis pipeline (https://github.com/james-cole/brainageR) previously described in detail. The pipeline includes the segmentation and normalisation of MR images with SPM12’s DARTEL toolbox. The quality of tissue segmentation was systematically assessed for all participants and no errors were found through visual inspection of segmentation output. After cerebrospinal fluid segmentation masking, preprocessed grey and white matter images were vectorised and concatenated. These data were then entered into a principal components analysis (PCA) to reduce dimensionality. Components for the top 80% of variance were used (n=435) for brain-age prediction in a machine-learning algorithm based on a pretrained Gaussian process regression model implemented in R package Kernlab. This model was trained on scans of 3377 healthy individuals from seven publicly-available datasets, and tested on 611 different scans of healthy individuals aged between 18-90 years. The model accurately predicted chronological age ($r = 0.95$, $R^2 = 67.24\%$, MAE = 4.9 years). As with other brain-age models, a proportional bias was observed where chronological age correlated with the difference between brain predicted and actual age ($r = -0.379$).

**Brain change control.** To control for between-patient differences in overall brain volume change following surgery we used SIENA, part of FSL. Brain and skull images were first extracted from the two-timepoint whole-head input data. The two brain images were then aligned to each other and resampled into a space halfway between the two. Tissue segmentation was then performed to identify non-brain/brain edge points. The perpendicular displacement of edges between the two timepoints was then estimated at these edge points. Using mean edge
displacement, a whole brain estimate of Percentage Brain Volume Change (PBVC) between the two timepoints was computed.

To ensure that the surgical cavity did not significantly bias the BrainAGE measurement, we also implemented an automated lesion-filling procedure previously tested in relation to BrainAGE in a large (n>500) multiple sclerosis cohort.

**Statistical analysis.** Statistical analyses were performed in R (v. 3.6.0). In Table 1, a Fisher’s exact test was used for categorical variables and an analysis of variance test for continuous variables to compare demographic differences between clinical outcome groups. All were non-significant (p>0.05) with the exception of sex which was included as a control variable along with age in subsequent statistical modelling.

BrainAGE was calculated as the brain-predicted age minus chronological age at the time of the MRI scan. As there was no evidence of non-normal distribution ($W = 0.98, p = .150$) and inhomogeneity of variance between groups ($\text{Fligner – Killeen:med} \chi^2(2) = 1.43, p = .489$) in the data, we used a linear multiple regression model to compare BrainAGE between controls and patient groups (SF, PS, left mTLE, right mTLE) both before and after surgery. Age was included as a covariate in all models to correct for the previously reported proportional bias, in addition to sex, grey matter, white matter and cerebrospinal fluid (CSF) brain volume. Figure 1 is a graphic representation of the study analysis pipeline. To directly compare BrainAGE before and after surgery within patient participants and across patient groups, we used a repeated measures mixed model with patients id included as a random effect and PBVC, resection size, age, sex and brain tissue volumes as control variables.
Standard protocol approvals, registrations, and patient consents. All patient and control participants provided written informed consent and the local ethics committee approved this study.

Data availability. The data that support the findings of this study are available via the corresponding author, on reasonable request.

Results

In accordance with the findings of previous work,\(^2^7\) we found that the difference between Brain\(\text{AGE}\) for unfilled and filled post-operative scans was also not significant in our data (mean difference = -0.79, 95% CI [-5.66, 4.09], \(t(37) = -0.33, p = .745\)), suggesting that the pipeline is robust to surgical cavity related bias. Figure 2 shows T1-weighted images (first row) before and after surgery for two patients, one with right- and the other with left-lateralized medial mTLE. The associated mask (CSF) and grey and white matter segmentations used in the computation of Brain\(\text{AGE}\) are also included for original (unfilled) and filled images. As the figure indicates, resections were appropriately masked out (see row 2) of grey and white matter segmentations in original images for all patients. Resections in filled images tended to be included in white matter segmentations. We therefore used Brain\(\text{AGE}\) computed from original images for the analysis.
Brain predicted age was highly correlated with chronological age ($r = .91$, 95% CI [.83, .95]) in controls with a mean absolute error of 4.08 years, comparable to the MAE found in the original training datasets (MAE=4.9). The mean ($\pm$SD) $BrainAGE$ in controls was 0.68 ($\pm$5.85) years. There was a significant correlation between $BrainAGE$ and chronological age in controls ($r = -.45$, 95% CI [−.67, −.14]) in line with the previously reported proportional bias.

Figure 3 shows group differences with estimation graphics implemented in dabestr. Data points are displayed as a swarmplot with effect size presented on an aligned axes as a 95% confidence interval (CI) calculated through bootstrap sampling (n = 5000). On average, patients with epilepsy showed an increased $BrainAGE$ of 7.97 years compared controls prior to surgery [95% CI = 5.26, 10.8] and an increase of 2.8 years following surgery [95% CI: 0.05, 5.78]. $BrainAGE$ differences between controls and patient sub-groups before surgery: SF = 8.71 [95% CI = 5.65, 12.3]; PS = 7.09 [95% CI = 3.69, 10.6]; left mTLE = 6.73 [95% CI = 3.58; 9.66]; right mTLE = 10.2 [95% CI = 7.03, 14.8]. $BrainAGE$ differences between controls and patient subgroups after surgery: SF = 3.37 [95% CI = 0.161, 7.07]; PS = 2.13 [95% CI = -1.31, 5.86]; left mTLE = 0.16 [95% CI = -2.78; 3.17]; right mTLE = 7.61 [95% CI = 4.45, 11.7]. Plots in Figure 3 show increased $BrainAGE$ in patients groups (PWE, SF, PS, left, right) compared to controls before, but not after surgery with greatest postoperative reduction occurring for patients with left mTLE.

The linear regression model used to evaluated group differences in baseline $BrainAGE$ (before surgery and correcting for age and sex, grey matter, white matter and CSF brain volume)
explained a significant and substantial proportion of variance ($R^2 = .60$, 90% CI [0.44, 0.68], $R^2_{adj} = .57$). Significantly higher BrainAGE was found for both SF ($b = 5.47$, 95% CI [2.70, 8.25]) and PS ($b = 4.69$, 95% CI [1.87, 7.50]) patient groups compared to controls. However, the estimation marginal means$^{30}$ indicated that BrainAGE difference between SF and PS was not significant ($t(76) = −0.52, p = .862$). Patient outcome groups were also not significantly different to controls using postoperative BrainAGE values (Model fit = $R^2 = .50$, 90% CI [0.32, 0.59], $R^2_{adj} = .46$); SF = $b = −0.07$, 95% CI [−2.90, 2.77]; PS = $b = −0.17$, 95% CI [−3.05, 2.71]). Though resection size did not differ between patient with left- and right-lateralised mTLE ($t(44) = −0.03, p = .976$), grouping patients by lateralisation again revealed higher BrainAGE before surgery for both groups compared to controls (left mTLE = $b = 3.72$, 95% CI [1.23, 6.21]; right mTLE = $b = 7.57$, 95% CI [4.62, 10.52]) and a significant left vs. right difference ($ΔM = −3.85$, 95% CI [−7.39, −0.31]). Following surgery, however, patients with right ($b = 7.46$, 95% CI [3.83, 11.09]) but not left ($b = 0.25$, 95% CI [−2.72, 3.23]) mTLE had significantly higher BrainAGE compared to controls, with marginal means estimation showing right vs. left difference to be more significant in postoperative BrainAGE ($ΔM = −7.20$, 95% CI [−11.71, −2.70]).

Put Figure 3 here.

Figure 4 shows paired mean difference estimation plot of BrainAGE for different patient groups. The average difference after compared to before surgery was -5.17 years [95CI = -6.53; -3.91]. The total explanatory power of the repeated-measures mixed model used to assess the effect of surgery on BrainAGE was substantial (conditional R2 = 0.87) and the part related to the fixed effects alone (marginal R2) was 0.31. As can be seen in the paired difference plot presented in Figure 4, the main effect of surgery was large with BrainAGE significantly higher ($M = 5.17$
years) before compared to after surgery (beta = 7.34, SE = 0.97, std. beta = 0.94, p < .001). The effect of outcome (SF-PS) was not significant (beta = -0.70, SE = 1.67, std. beta = -0.09, p = 0.677), though a trend emerged when only patients with continuing seizures with loss of awareness (ILAE 3-6) were included into the PS group (beta = -3.05, SE = 1.61, p = 0.065). The interaction effect of surgery and outcome was not significant (PS = ILAE 2-6: beta = -0.80, SE = 1.24, std. beta = -0.10, p = 0.519; PS = ILAE 3-6: beta = -0.39, SE = 1.35, std. beta = -0.05, p = 0.773). The main effect of lateralisation (right/left mTLE/surgery) was large and significant with an overall increased BrainAGE associated with right lateralisation (beta = 8.05, SE = 1.58, std. beta = 1.05, p < .001). The interaction between surgery (BrainAGE before and after) and lateralisation was also significant, indicating significantly less postoperative BrainAGE reduction for right compared to left mTLE (beta = -3.71, SE = 1.22, std. beta = -0.48, p < .01). The main effect of resection size on BrainAGE was not significant (beta = 0.75, SE = 0.80, std. beta = 0.10, p = 0.347) and there was a small positive effect of PBVC (beta = 1.00, SE = 0.48, std. beta = 0.21, p < .05). Other variables such as age of seizure onset, years from onset to surgery, surgery access, seizure frequency and burden were removed from the final model due to minimal and non-significant effects on BrainAGE.

Discussion

In this study we used a brain predicted age measure to investigate the effects of epilepsy surgery on overall brain health. Preoperatively, patients showed an increased BrainAGE (difference between brain predicted and actual age) of more than seven years compared to controls. However, surgery was associated with a BrainAGE reduction of an average of five years irrespective of whether the procedure resulted in seizure freedom. This post-operative
reduction was particularly pronounced for patients with left lateralised mTLE where *BrainAGE* values following surgery resembled those of controls.

Given the correlation between *BrainAGE* and cognitive decline, the postoperative normalisation of *BrainAGE* is consistent with literature that shows restoration of some aspects of neuropsychological function following successful epilepsy surgery. This has been observed in domains including verbal fluency, IQ, executive functioning, and attention, despite an increased risk to verbal memory associated with residual function in resected regions. The imaging literature also provides evidence for neuroplastic network changes with restorative potential. In a longitudinal functional MRI study, plasticity of a working memory network was observed after temporal lobe surgery. Another study examining functional connectomes in the brainstem found that connectivity patterns of patients were more likely to resemble those of controls after epilepsy surgery. Other research, however, shows a limited impact of the procedure on functional and structural brain networks, and that connectivity normalisation is associated with whether or not a patient becomes seizure free as a result of neurosurgery.

We expected that patients who were rendered completely seizure free (ILAE 1) would have lower *BrainAGE* compared to patients with persistent postoperative symptoms (ILAE 2+). However, there was no significant difference between clinical outcome groups. Postoperative cognitive and quality-of-life outcomes are influenced by many factors and only partly depend on seizure control. *BrainAGE* may therefore reflect surgery-related changes that are not directly associated with seizure status. Furthermore, following the majority of previous epilepsy cohort studies, we used a dichotomous outcome grouping (ILAE 1 vs ILAE 2+) that does not account for the considerable cumulative reduction in seizures for patients in the ILAE 2+ (PS) group. Notably, we did find was a borderline difference between patients rendered seizure free and only those who continued to experience debilitating postoperative seizures (ILAE 3-5), suggesting
that there may in fact be a subtle relationship between BrainAGE and seizure outcome that may be difficult to detect in relation to surgery due to the personal improvements in seizure control that patients are likely to experience following surgery (a ILAE 3 patient who previously had a seizure a day will be a relative clinical success). Though we did not have access to patients’ seizure outcome in response to anti-seizure medication before surgery, it may be that BrainAGE reduction is more closely related to the difference between seizure outcome after compared to before surgery. Without information on postoperative anti-seizure medication it was also not possible to disentangle the effects of surgery from medication on seizure outcome. However, this does not have implications for our findings, as medication is not likely to have been significantly altered during the short period between pre- and post-operative scans (mean 1.96 years, SD 0.92).

Though we controlled for postoperative volume change and resection size in our statistical modelling we cannot exclude the possibility that BrainAGE reduction may be a by-product of invasive surgery and unrelated to increased brain resilience. However, a supplementary analysis revealed that there was no significant BrainAGE difference between postoperative scans with artificially filled and unfilled resections, in accordance with a previous large-scale MS study, suggesting that the measure may capture features associated with brain-wide correlates of surgery beyond those relating to presence of the surgical cavity. The link between post-surgery BrainAGE reduction and brain resilience could be more reliably established in future studies if a strong relationship between BrainAGE reduction and positive cognitive and quality-of-life outcomes is observed in a study with more postoperative scans to maximise the generalisability of study results. It may also be possible to isolate the BrainAGE correlates of surgery specifically related to TLE through comparison with a patient group without TLE that have undergone equivalent surgery treatment.
More generally, our results support the proposal that mTLE is related to morphological changes of accelerated aging, in accordance with evidence associating the disorder to neurodegenerative features such as neuronal loss in and around the disease epicentre, axonal sprouting, blood-brain barrier leakage, loss of brain plasticity and reserve capacity, and increased inflammation. The extent of the BrainAGE increase (7.9 years) in patients before surgery found in our study is also consistent with previous epilepsy brain-age studies that show comparable effects of between 4.5 to 10.9 years in focal epilepsy cohorts. These findings are in line with clinical and epidemiological studies that highlight the benefits of earlier epilepsy surgery interventions over prolonged medical therapy.

Our findings showed that patients with left mTLE were more likely to have normalised BrainAGE after surgery relative to patients with right mTLE, though no difference was found in resection size between left and right surgery. This is an additional novel finding and we can only speculate on the reasons why there is a lateralisation difference. Surgery aside, it is well demonstrated that patients with left and right mTLE have different distributions of brain abnormalities: patients with left mTLE are frequently reported to have a more bilateral and widespread distribution of brain alterations relative to patients with right mTLE as well as a more intense progression of white and grey matter atrophy. A systematic review of neuropsychological outcomes after epilepsy surgery showed that the greatest rate of improvement across all domains occurred in verbal fluency with left-sided temporal surgery. It has also been reported that surgery reduces mortality associated with refractory mTLE but only in patients with left-sided surgery. The same work indicated that mortality was not related to postoperative seizure outcome. In fact, there is little evidence to suggest that side of surgery is related to seizure outcome. Given the established link between BrainAGE and increased mortality, our findings which should be taken as preliminary leave open the possibility that
surgery may have particular benefits for patients with left mTLE, though confirmation would require a targeted investigation that also measures surgery-related neuropsychological changes.

Current BrainAGE algorithms are likely to improve in the future using larger training datasets and by taking advantage of multimodal imaging (e.g., T2- and diffusion-weighted MR sequences). It is also not yet clear what 3D T1-weighted image features most reliably contribute to the BrainAGE measure and further methodological work in neurotypical and clinical populations is needed to better understand how it reflects the non-linear patterns of age-related changes including regional brain volume reductions. Given that there is a known pattern of cerebral (particularly limbic) atrophy in TLE\(^1,2\), and that decreasing brain volume is a characteristic of aging\(^3\), then increasing atrophy in TLE may drive greater BrainAGE. However, the factors that suggest a ‘recovery’ of increasing BrainAGE after surgery is currently unknown.

However, reliance on largely standardised MR images allows the method to be widely applicable in clinical settings where the sequence is acquired for all patients referred to epilepsy surgery programs. Based on our findings, brain-predicted age models have the potential to further risk stratify patients that will benefit from epilepsy surgery, thereby improving the personalised medicine approach for people with refractory epilepsy in conjunction with other imaging and neuropsychological screening tools.\(^4\) Furthermore, given that increased BrainAGE is an independent predictor of mortality,\(^12\) the imaging biomarker may be used to identify patients at high risk of sudden unexplained death in epilepsy. Brain-age models may play both a prognostic and diagnostic role in the neurocognitive and psychiatric disorders associated with epilepsy as these have proven to be useful in the context of psychiatric disease and impaired
cognition.\textsuperscript{11,49} Other advances in deep learning applied to brain images are beginning to play a role in clinical decision-making, such as in the automatic classification and prognostics of TLE.\textsuperscript{50}

In conclusion, our study found that epilepsy surgery was associated with reduced brain imaging defined age, suggesting that some morphological brain changes linked with accelerated aging in mTLE may be reversible. This is consistent with studies that found neuropsychological improvements following surgery and those calling for earlier surgical intervention where medical therapy is ineffective. Models of brain-predicted age may provide insight into the treatment and prognosis of epilepsy.
### Appendix 1. Authors

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<tr>
<th>Name</th>
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<tr>
<td>Christophe E de Bézenac, PhD;</td>
<td>University of Liverpool, UK</td>
<td>Design and conception of study, analysis of data, drafting manuscript</td>
</tr>
<tr>
<td>Guleed Adan; MD;</td>
<td>University of Liverpool, UK</td>
<td>Design and conception of study</td>
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<tr>
<td>Bernd Weber MD, PhD;</td>
<td>University of Bonn, Germany</td>
<td>Design and conception of study</td>
</tr>
<tr>
<td>Simon S. Keller, PhD</td>
<td>University of Liverpool, UK</td>
<td>Design and conception of study, drafting manuscript</td>
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### References


**Table 1.** Clinical demographics.

Clinical demographics for 48 mTLE patients that underwent surgery. Patients are divided between those that became seizure free (SF) and had persistent seizures (PS) following surgery.
P-values were determined by a Fisher’s exact test for categorical variables and an analysis of variance test for continuous variables.

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In addition to clinical patient data, 3D T1-weighted MRI scans were acquired for 48 patients with mTLE before and after temporal lobe surgery and for 37 controls (top left panel). Brain-age was estimate for each scan using a trained gaussian processes regression (GPR) model following tissue segmentation, vectorization and principle component analysis-based dimension reduction (PCA). BrainAGE was computed as brain-predicted age minus actual age (middle panel).

BrainAGE comparisons were made between patients and control groups before and after epilepsy surgery, controlling for percentage brain volume change (SIENA, B), age and sex (D).
**Figure 2.** T1-weighted images (first row) before and after surgery for two patients, one with right- and the other with left-lateralized medial mTLE. Below the associated masks (CSF) and grey and white matter segmentations used in the computation of BrainAGE are included for original (unfilled) and filled images following surgery. Resection location is indicated by a red arrow for original images used in the analysis.
**Figure 3. Between-group comparisons of BrainAGE.**

Comparisons of BrainAGE (computed as brain-predicted age minus actual age) for patients with epilepsy (PWE) and healthy controls (HC) (A, D), patient that are seizure free (SF) and those with persistent seizures (PS) following surgery (B, E), and left- and right-sided mTLE (C, F). Comparisons are presented with BrainAGE values before (A, B, C) and after (D, E, F) surgery. In A and D, raw data points for BrainAGE in HC and PWE are shown in the left panel with unpaired group difference estimations plotted as a bootstrap sampling distribution (n = 5000) (shaded area). Average effect size (mean difference) is depicted as a black dot and the 95% confidence interval indicated by the ends of the vertical error bar. In B, C, E and F, raw data for patient sub-groups are compared to HC (red) and plotted/colour coded on the upper panel with associated estimation plots shown below. Note that where the 95% confidence intervals (error bars) cross the horizontal line at zero, an effect size equal to zero is possible, i.e., no reliable difference to HC.
Figure 4. The effects of epilepsy surgery on BrainAGE.

Paired difference of BrainAGE (computed as brain-predicted age minus actual age) before and after epilepsy surgery in patients with medial Temporal Lobe Epilepsy (mTLE). Colours indicate patient sub-groups (PS = persistent seizures; SF = seizure free; left = left mTLE; right = right mTLE). Paired difference are shown on the right with confidence plotted as a randomised bootstrap sampling distribution (n = 5000) (shaded area) and the average effect size depicted as a black dot and the 95% confidence interval indicated by the ends of the vertical error bar.
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