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The potential compensatory effect of transcranial electrical stimulation on the adverse impact of white matter damage in the aging brain

Dear Editor,

The increase of white matter hyperintensities (WMH) is a concomitant alteration of brain aging, indicative of localized white matter damage [1–4]. WMH as whole-brain total white matter lesion volume represent white matter damage in terms of demyelination, axonal and glial loss, neuroinflammatory processes, along with a disruption of long-range connections in the brain of older adults with or without cognitive impairment [2]. The functional significance of WMH has been demonstrated in different cognitive domains, indicating that higher individual lesion volume is associated with lower executive, memory, and attention performance [3]. A recent study examined the link between lesion volume and behavioral changes induced by a three-month cognitive training intervention in older adults, observing that higher WMH at baseline were associated with reduced gains in processing speed [1]. The findings of this study indicated a potential prognostic value of individual white matter damage on training-induced cognitive plasticity in the aging brain. Whether or not white matter damage is related to brain stimulation-induced cognitive plasticity has not yet been reported.

So far, some evidence has demonstrated an impact of white matter damage on individual electric fields induced by transcranial electrical stimulation (tES) [5,6]. By estimating electric field distributions using magnetic resonance imaging (MRI)-derived finite element models in older adults, Indahlastari and her colleagues observed an association between current density and age-related total lesion volume, indicating that the inclusion of WHM in individual electric field models may increase their accuracy [5]. Further, considering WMH in tES interventions may be mostly relevant in populations with greater white matter lesion volume due to aging or other pathologies [5,6].

Here, we aimed to explore the potential role of age-related white matter damage for tES-induced performance gains in older adults. We used data from two of our recent randomized controlled trials that investigated the effects of a combined tES-plus-training intervention in older adults on the continuum from healthy aging to mild cognitive impairment [7,8]. All participants underwent a three-week cognitive training (consisting of a letter updating and a decision-making task) combined with either anodal (1 mA, 20 min during each of the nine training sessions) or sham transcranial direct current stimulation (tDCS) over the left dorsolateral prefrontal cortex [7,8]. Comparisons of anodal and sham tDCS groups revealed no difference in training tasks, but overall superior working memory performance gains as evident in the N-back task in the anodal tDCS groups [7,8]. For the current analysis, we used the MRI data acquired before the intervention (at baseline) as well as individual performance gains in the N-back task. For the quantification of WMH, a 3D Fluid-Attenuation-Inversion-Recovery-image (FLAIR; 1 mm^3 isotropic voxel, TR: 5000 ms, TE: 388 ms, TI: 1800 ms, FOV: 250 × 250 mm, 160 sagittal slices) and a 3D T1-weighted image (1mm^3 isotropic voxel, TR = 2300 ms, TE = 2.96 ms, inversion time = 900 ms, flip angle = 9°, 256 × 240 × 192 mm^3 matrix) were analyzed. WMH were automatically detected using FSL BIANCA based on the k-nearest neighbor algorithm, creating a probability WMH mask by classifying voxels based on intensity and spatial features [8]. Lesion volume was then calculated in the subject-space, binarizing masks at a recommended threshold of 0.9 to avoid an overestimation (i.e., false positive classification) of WMH volume [9]. FLAIR data were available from a total of 87 older adults (32 females; mean ± SD age: 69 ± 4 years). A frequency map of the WMH was created for visualization of the whole-brain white matter lesions in our sample (Fig. 1A). Statistical analyses were conducted in R [10]. WMH were log-transformed to account for skewness. Performance gains were operationalized by the change of post-minus-pre-intervention % correct responses in the 2-back condition of the N-back task [7,8]. In order to link WMH to individual performance gains, linear regression model analyses were conducted, adjusted for sex and FreeSurfer-generated estimated total intracranial volume [11].

We observed a significant effect of WMH on performance gains ($\beta = -0.14$, 95%-CI [−0.25, −0.03], $p = 0.01$), pointing towards an association between higher WMH with lower gains as well as a potential interaction between WMH and stimulation group ($\beta = 0.11$, 95%-CI [−0.05, 0.27], $p = 0.17$). Explorative analyses of the interaction by marginal means revealed that performance gains differed between groups for individuals with higher WMH (at 75th percentile of WMH (3.6): anodal: $\beta = 0.08$ [0.03, 0.13], sham: $\beta = -0.05$ [−0.05, 0.04], $p = 0.01$; at 25th percentile (3.2): anodal: $\beta = 0.09$ [0.04, 0.14], sham: $\beta = 0.05$ [−0.002, 0.10], $p = 0.24$). To further illustrate the direction of this interaction, we performed Pearson's correlation analyses and bias estimation using bootstrapping (anodal: $r = -0.01$, $p = 0.9$; bias corrected coefficients: $r_{cor} = -0.01$ [−0.33, 0.31], sham: $r = -0.35$, $p = 0.01$; bias corrected coefficients: $r_{cor} = -0.35$, [−0.57, −0.07]). The results suggest that a link between WMH and performance gains only emerged for the sham group, indicating that performance gains in the anodal tDCS group were independent from WMH volume.

The current analyses revealed that the presence of WMH volume negatively influences the effectiveness of cognitive training in older adults. This suggests that greater WMH volumes correlate with diminished benefits from the intervention, consistent with prior research indicating reduced cognitive plasticity in those with more significant white matter damage [1]. Our results further showed that the inverse relationship between WMH and performance gains was only present in the group of older adults who received sham tDCS. Thus, interestingly, the predictive role of WMH volume disappears when anodal tDCS is combined with the cognitive intervention. This lack of impact of white matter damage on cognitive plasticity in the anodal tDCS group may

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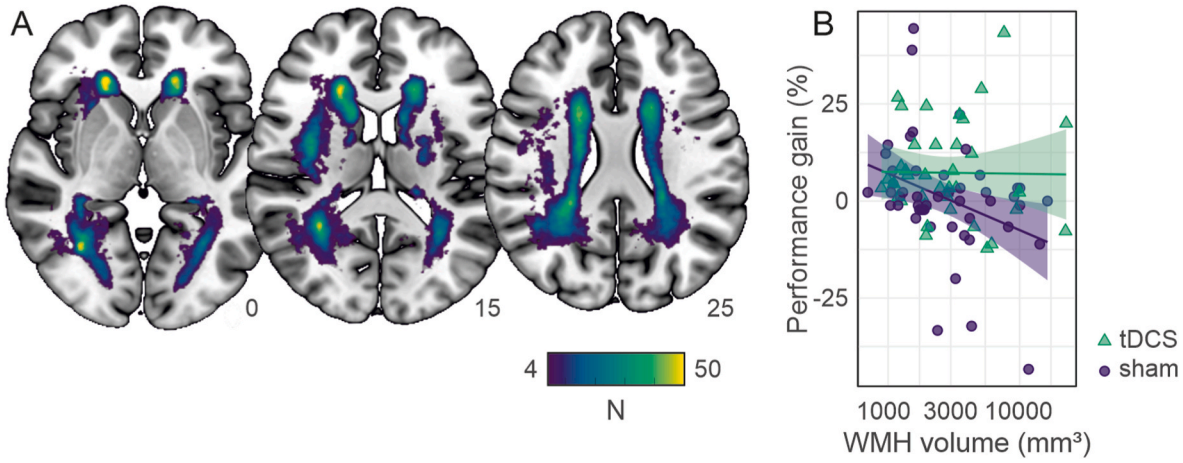

Fig. 1. A Frequency maps of the white matter hyperintensity (WMH) mask, overlaid on the Montreal Neurological Institute (MNI) brain, created with MRIcroGL (https://www.nitrc.org/projects/mricrogl). Individual WMH masks from all participants were normalized, converted to binary images and then summed (color coding reflects the number of participants). **B** Scatter plot illustrating the association between performance gain (change of post-minus-pre-intervention % correct in the 2-back condition of the N-back task) and (log-transformed) WMH volume in mm^3 in anodal (green; n = 38) and sham (purple; n = 49) group. tDCS, transcranial direct current stimulation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

suggest a compensatory effect of tDCS.

In sum, this is the first exploratory analysis of a link between WMH volume and tDCS-induced performance gains. Among various baseline characteristics with impact on interventional outcomes in the aging brain, WMH has only recently gained attention, reflecting that age-related brain tissue alterations such as demyelination, axonal and glial loss may mediate the effects of plasticity-inducing interventions [1,5]. Our findings extend these initial reports by observing a potential compensatory effect of tES on the adverse impact of WMH volumes. Thus, white matter damage might be a significant biomarker, predicting the individual benefit of tDCS-accompanied cognitive training intervention. In addition to a predictive value of baseline WMH of tDCS responsiveness, which was the focus of the current analysis, tDCS may have an impact on white matter damage itself (e.g., by reducing neuroinflammatory responses [12–14]). Further research is needed to uncover the role of white matter integrity on brain stimulation response and its modulation in the human brain.

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CRediT authorship contribution statement

Anna E. Fromm: Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Formal analysis, Conceptualization. **Daria Antonenko:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

None.

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