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Cortical and subcortical responsiveness to intensive adaptive working memory training: An MRI surface-based analysis

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Abstract

Working memory training (WMT) has been shown to have effects on cognitive performance, the precise effects and the underlying neurobiological mechanisms are, however, still a matter of debate. In particular, the impact of WMT on gray matter morphology is still rather unclear. In the present study, 59 healthy middle-aged participants (age range 50–65 years) were pseudo-randomly single-blinded allocated to an 8-week adaptive WMT or an 8-week nonadaptive intervention. Before and after the intervention, high resolution magnetic resonance imaging (MRI) was performed and cognitive test performance was assessed in all participants. Vertex-wise cortical volume, thickness, surface area, and cortical folding was calculated. Seven subcortical volumes of interest and global mean cortical thickness were also measured. Comparisons of symmetrized percent change (SPC) between groups were conducted to identify group by time interactions. Greater increases in cortical gyrification in bilateral parietal regions, including superior parietal cortex and inferior parietal lobule as well as precuneus, greater increases in cortical volume and thickness in bilateral primary motor cortex, and changes in surface area in bilateral occipital cortex (medial and lateral occipital cortex) were detected in WMT group after training compared to active controls. Structural training-induced changes in WM-related regions, especially parietal regions, might provide a better brain processing environment for higher WM load.

KEYWORDS

aging, brain plasticity, *n*-back, surface-based analysis, working memory training

1 | INTRODUCTION

Working memory (WM), the ability to simultaneously retain and manipulate information with limited capacity, is a core component of executive functions that, in turn, are essential for daily life functioning (e.g., planning, reading, typing, etc.) (Baddeley, 1992; Diamond, 2013). WM capacity has been closely linked to other higher-level cognitive functions (such as, e.g., reasoning skills or fluid intelligence; Johnson et al., 2013; Suss, Oberauer, Wittmann, Wilhelm, & Schulze, 2002). Given global aging and the decrease of WM with increasing age

(McNab et al., 2015), as well as considering the important impact of WM on quality of life in elderly population, especially older adults with age-related diseases (e.g., cognitive impairments and dementia), techniques to preserve and improve WM performance are gaining increasing importance. Hence, it comes as no surprise that there is a rising interest in studying the effects of WM training programs to improve WM capacities and cognitive performance in general. And indeed, some studies showed that WM training induced improvements in WM (i.e., trained tasks) as well as in untrained tasks (e.g., inhibition performance or fluid intelligence; Au et al., 2015;

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Borella, Carretti, Riboldi, & De Beni, 2010; Dunning, Holmes, & Gathercole, 2013; Jaeggi, Buschkuhl, Jonides, & Perrig, 2008; Zinke et al., 2014).

Previous imaging studies have identified structural plasticity of gray matter as a consequence of learning or training (Draganski et al., 2004; Kuhn, Gleich, Lorenz, Lindenberger, & Gallinat, 2014; Zatorre, Fields, & Johansen-Berg, 2012), even in the elderly (Jiang et al., 2016; Kuhn et al., 2017; Lampit, Hallock, Suo, Naismith, & Valenzuela, 2015). However, effects on gray matter structure induced by WMT have been investigated only by a limited number of studies up to now, and studies in healthy elderly are even scarcer. In one of these studies, researchers observed reduced gray matter volume in frontoparietal regions after 5 days of mental calculation training in a healthy young population (21.7 ± 1.4 years) (Takeuchi et al., 2011). In a more recent study, Colom et al. (2016) reported increased gray matter volume in posterior cingulate, the cerebellum, and the temporal lobe after a 12-week adaptive WMT compared to a passive control training. Using surface-based analysis with a-priori ROIs on the same dataset, they found significant changes of cortical thickness (CT) in ventral frontal and middle temporal cortex, and significant changes of cortical surface area (CSA) in the posterior temporal cortex and pars opercularis in the training group relative to the passive control group (Roman et al., 2016). Notably, both of the studies were based on young healthy populations with restriction to female undergraduates (mean age 18 years), therefore the findings were not comparable to other populations (e.g., male participants or other age groups). Furthermore, the findings may not generalize to more natural environments (e.g., training at home) because participants were trained under laboratory supervision. A study by Engvig et al. (2010) based on a healthy elderly cohort (mean age 61 years) showed cortical thickening in right fusiform and insula in a trained group after an 8-week WMT together with cortical thinning in a passive control group. Using a-priori ROIs, Metzler-Baddeley, Caeyenberghs, Foley, and Jones (2016) observed WM training-related increases in CT in right caudal middle frontal cortex as well as volume increases in left pallidum, while CT decreased in the right insula. In contrast, another recent study (age range of participants: 18–40 years), also ROI-based, failed to find training-induced gray matter plasticity (i.e., in terms of gray matter volume, CT and CSA) after a 6-week *n*-back WMT (Lawlor-Savage, Clark, & Goghari, 2019).

CT and CSA have different genetic backgrounds and underlying cellular mechanisms as well as different developmental trajectories (Panizzon et al., 2009; Wierenga, Langen, Oranje, & Durston, 2014). Several studies reported a weak genetic correlation between CSA and CT and multiple variants were found to be associated with either surface area or CT (Eyler et al., 2011; Hofer et al., 2018; Rimol et al., 2010; Winkler et al., 2010). CT, which is related to radial neuronal migration, is influenced by the number and size of cells within a column, as well as by the density and arrangement of the cells. In contrast, surface area of a given area is associated with the number of cellular columns (Chenn & Walsh, 2003; Rakic, 1995, 2009). Therefore, studying CSA and CT, in addition to gray matter volume, provides a more comprehensive picture of the potential effects of WMT.

Compared to voxel-based morphometry which combines two relatively independent measurements (i.e., thickness and surface area) influenced by different factors to calculate gray matter volume (Panizzon et al., 2009), this surface-based approach aids in understanding cortical changes beyond the basic volumetric changes by enabling separate measurement of CT and CSA as well as cortical folding (Winkler et al., 2010). Moreover, the surface-based method addresses some of the limitations and methodological problems inherent to voxel-based morphometry (e.g., significantly higher accuracy in registration than any form of volume-based registration; Ghosh et al., 2010; Montal et al., 2018). In addition, surface-based methods allow the assessment of cortical folding—a highly sensitive parameter that has not yet been investigated with regard to WMT induced plasticity. Cortical folding can be characterized by the local gyrification index (LGI; Schaer et al., 2008; Zilles, Palomero-Gallagher, & Amunts, 2013) and has been demonstrated to be associated with cognitive abilities and aging (Gregory et al., 2016; Lamballais, Vinke, Vernooij, Ikram, & Muetzel, 2020). In addition, abnormalities in cortical folding are also associated with psychiatric and neurodegenerative diseases (Nunez et al., 2020; Sallet et al., 2003; Schmaal et al., 2017).

Taken together, the effects of WMT on gray matter structure have not been thoroughly explored, especially amongst middle-aged and elderly people. Previous evidence for training-induced macrostructural effects remains inconsistent and controversial. Heterogeneous approaches (e.g., training tasks, training duration, training intensity, training location, training supervision, active vs. passive control group, voxel-based vs. surface-based methods, a-priori ROIs vs. whole brain approaches) and populations (e.g., specific age groups, pure male/female cohorts) may explain these inconsistencies to some degree and point to a need for more empirical evidence based on well-controlled studies.

Against this background, we employed both cognitive and structural measures to investigate the effects of an 8-week WMT compared to an active control training in a group of middle-aged adults with specific age range (50–65 years old). We chose this age group for several reasons. First, neural plasticity changes across the life-span and significantly decreases at old age. Second, aging is the main risk factor for cognitive impairments and neurodegenerative diseases (e.g., dementia). Thus, early prevention measures are necessary to protect the brain from age-related damages and the chosen age range seems optimal for an early but not too early prevention. Thus, training in middle-aged individuals can be regarded as more promising than training in older adults, given a relatively intact cognition and a lack of significant atrophy in this restricted age group thus excluding potentially confounding effects on WM-related neural plasticity. On the behavioral level, training-related effects on cognition were investigated by comparing cognitive performance before and after the interventions. On the imaging level, we employed surface-based analyses and investigated changes in four characteristics (CT, cortical volume [CV], CSA, and LGI) as well as subcortical volumes to investigate the neuroplastic effects of WM training on gray matter structure. Although some of these measures may covary, they reflect different aspects of gray matter structure and were

expected to be affected by intensive WM training (Bajaj et al., 2018; Lamballais et al., 2020).

2 | MATERIALS AND METHODS

2.1 | Participants

Participants were recruited via bulletin board in the hospital or online advertisements. All volunteers underwent a screening evaluation prior to enrollment based on the following cognitive and neuropsychiatric screening tests: the Mini-International Neuropsychiatric Interview (M.I.N.I.), the short form of the geriatric depression scale, the Mini-Mental State Exam (MMSE), the Clock Drawing Test (CDT), and Edinburgh Handedness Inventory (EHI; Agrell & Dehlin, 2012; Burke, Roccaforte, & Wengel, 1991; Folstein, Folstein, & McHugh, 1975; Sheehan et al., 1998; Veale, 2014). Participants were included in our project based on the following inclusion criteria: (1) no neurological illness or psychiatric disorder; (2) no cognitive deficits; (3) no contraindication to magnetic resonance imaging; (4) right-handedness; (5) German speakers; (6) medication naïve during the study. Participants were pseudo-randomly single-blinded allocated to the working memory training (WMT) group or active control group (gender- and age- matched). Finally, a group of 59 participants (age range: 50–65 years, mean \pm SD: 55.79 \pm 4.2) was included in the current analysis (see Figure 1).

All participants were informed about the purpose of this study and written informed consent was provided by each participant. The

study was approved by the federal office for radiation protection as well as the Ethics Committee of the Klinikum Rechts der Isar, Technische Universität München.

2.2 | WMT procedure

The *n*-back task paradigm, in which participants are presented a sequence of stimuli one by one and they need to give response if the current stimulus is the same as the one presented *n* items earlier, was used as training program in our study. Both the WMT group and the active control (CON) group performed two different training paradigms (verbal and visual tasks) over 8 weeks (~20 min per training session, four sessions per week, restriction of only one training session per day). The order of visual and verbal tasks was counterbalanced between participants in each group. The online training was carried out using the Inquisit Software on participants' own computers at home. After each training session, training data of each participant were saved in logfiles which were automatically uploaded to the Millisecond Software website (<https://www.millisecond.com/>). The training status as well as performance were checked and a weekly training progress report was sent to each participant via email.

In the WMT group, participants performed an adaptive *n*-back paradigm comprising nine blocks in each training session (i.e., they all started with 1-back level and the final level varied depending on participant's performance) for both visual and verbal tasks, which means the *n*-back level increased or decreased adaptively depending on participant's performance and the highest *n*-back level was set to 9 (Jaeggi et al., 2010).

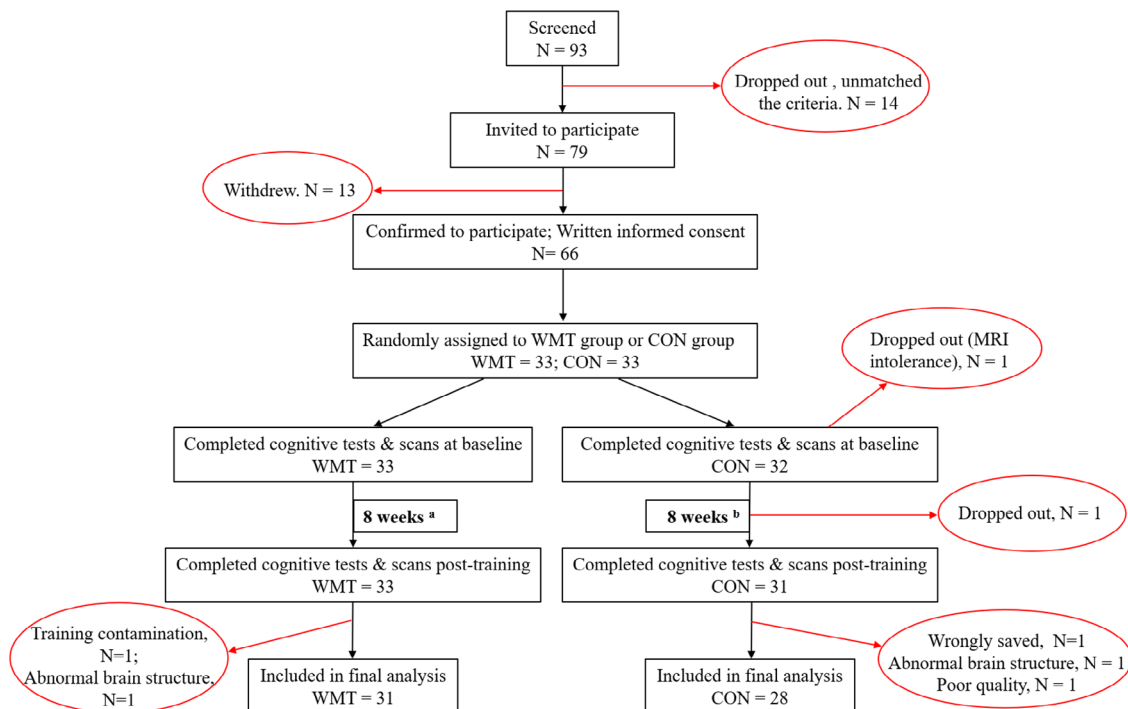


FIGURE 1 Flow chart of the study design. CON, control training; WMT, working memory training; ^aadaptive *n*-back task training; ^bnonadaptive *n*-back task training

Specifically, the *n*-back level increased by one in the next block if the percentage of correct answers exceeded 90%, the *n*-back level decreased if accuracy was below 80%. Otherwise, the *n*-back level stayed the same. The training in the CON group was nonadaptive, meaning participants only performed fixed low-level training (i.e., 1-back verbal task and X-back visual task). Thus, the X-back visual task was a pure attentional task in which participants needed to respond whenever the target shape was presented. The instruction for the target shape was shown at the beginning of each X-back block.

2.3 | Cognitive test battery

All participants completed a battery of nine cognitive tests before and after training to investigate potential near or far transfer effects (see Supporting Information for details of all cognitive tests). In another manuscript currently under submission, we are reporting and discussing the results of all cognitive tests in detail. Briefly, the results showed that a significant group by time interaction was only observable in the Digit Span Test (forward). The Digit Span Test is a subtest of HAWIE-R (Tewes, 1994) which is the German version of the Wechsler Adult Intelligence Scale (WAIS) and measures verbal WM as well as storage capacity. Thus, in the current study, we only included the Digit Span Test to explore a potential relationship between training-induced structural changes and training induced verbal WM changes. The number of correct answers was taken as the outcome measure and was correlated with the different structural characteristics extracted from the significant clusters reported above (for more details, refer to the Section 2.5).

2.4 | MRI acquisition and processing

2.4.1 | Image acquisition

Imaging data were collected on a 3T hybrid PET/MR Siemens Biograph mMR scanner with a vendor-supplied 16-channel head coil at the Klinikum rechts der Isar, Munich, Germany. High resolution structural images of all subjects were acquired by using a three-dimensional, T1-weighted magnetization prepared—rapid gradient echo (MP-RAGE) sequence. The sequence parameters were: time of repetition (TR) = 2,300 ms; echo time (TE) = 2.98 ms; flip angle (FA) = 9°; field of view (FOV) = 256 mm; matrix size = 256 × 240 mm; slice thickness = 1.0 mm (no gap); voxel size = 1.0 × 1.0 × 1.0 mm³ and 160 sagittal slices. In addition, PET images, functional images, and diffusion tensor images were acquired in the same scanning session (results reported elsewhere, for task-based functional results, refer to Emch, Ripp, et al. (2019)).

2.4.2 | Image preprocessing

All subjects' T1 images were evaluated by a medical specialist to assess the presence of abnormal structural features. Two subjects

were excluded because of extensive calcification (see Figure 1). All images were inspected visually in MRIcron for motion-related artifacts (e.g., ghosting, blurring, and stripping). Anatomical reconstruction of the cortical surfaces and volumetric segmentation were performed using FreeSurfer imaging analysis suite (Version 6.0.0, <https://surfer.nmr.mgh.harvard.edu>) following the longitudinal processing stream as previously described (Reuter & Fischl, 2011; Reuter, Rosas, & Fischl, 2010; Reuter, Schmansky, Rosas, & Fischl, 2012). Briefly, several preprocessing steps such as motion correction, skull stripping, registering the images to Talairach space as well as gray and white matter segmentation were completed for both timepoints of all subjects independently. Then, for each subject both timepoints were used to create an unbiased robust within-subject template (Reuter et al., 2012). Finally, the longitudinal processing of each time point was initialized with the information from the above steps to reduce variability across time and increase statistical power. The reconstructions were visually inspected and where necessary, corrected manually (e.g., boundaries found to be inaccurate upon visual inspection were corrected manually).

When all the reconstructions were completed, the reconstructed surfaces were used to calculate CT, CSA, and CV. The CT is defined as the shortest distance between gray-white boundary (white surface) and gray-cerebrospinal fluid interface (pial surface), whereas CSA (the total area of the surface encompassing a brain region) was calculated as the sum of the area of the vertices within a given region on the white surface (Winkler et al., 2012). The LGI, a validated method incorporated into FreeSurfer, was calculated as the ratio of the folded pial surface (25 mm radius circular region of interest) to the surface of the corresponding smoothed outer surface by using surface-based, 3D gyrification measurements (Schaer et al., 2008). LGI reflects the complexity of folding at a given pial surface, and LGI values can range between 1 and 5, the greater value of LGI, the more amount of cortex buried in the sulcal folds (Schaer et al., 2012).

In addition, during the above preprocessing, volumes of seven subcortical regions of interests (ROIs), including thalamus, putamen, caudate nucleus, pallidum, amygdala, hippocampus, and nucleus accumbens, were obtained for volumetric measures implemented in FreeSurfer. Caudate, putamen, pallidus, and nucleus accumbens are main parts of basal ganglia which are involved in WM maintenance (Moore, Li, Tyner, Hu, & Crosson, 2013). Moreover, cortico-basal ganglio-thalamic loops are involved in learning, WM control and response selection (Schroll, Vitay, & Hamker, 2012). The amygdala-hippocampus complex plays a vital role in encoding and consolidation of memory as well as regulating learning (Richter-Levin & Akirav, 2000).

Finally, we assessed the global CT within the left and right hemispheres which was obtained from the “mean thickness” variable provided by FreeSurfer, which is calculated by using the total thickness below the pial surface subtracted by the total thickness below the white surface (Fischl & Dale, 2000).

Volumes of subcortical regions and the global CT values were extracted and then analyzed using SPSS 19.0 (IBM Corporation, Somers, NY).

2.5 | Statistical analyses

Normal distribution of all demographic and behavioral data, as well as the mean thickness and all subcortical volumes was tested using the Kolmogorov–Smirnov test.

Demographic data at baseline were analyzed using chi-square (gender) or independent sample *t*-tests (age), which were carried out with SPSS 19.0 (IBM Corporation, Somers, NY).

The training data were analyzed with SPSS 19.0 using two-tailed paired *t*-test between the means of first four sessions and the mean of last four sessions for *d* prime (*d'*) (Macmillan & Creelman, 2004) values for each group and each WM modality (e.g., verbal and visual) separately. *D* prime (*d'*), a discriminability index, is calculated from the difference between *Z* transformed hit rate and false-alarm rate ($d' = ZHit - ZFA$; Haatveit et al., 2010). Compared to accuracy values, *d'* is a more precise indicator and bias free, because *d'* considers both “hits” and “false alarms” by calculating the standardized distance between the probability distributions of target present and target absent. Higher *d'* represents better performance in terms of higher response accuracy (i.e., fewer misses or false alarms). For WMT group, in addition to *d'*, we also computed two-tailed paired *t*-test between the mean achieved *n*-back level of the first four and last four sessions for verbal and visual training respectively. As two last sessions of two participants (one in CON group and one in WMT group) were lost due to technical reasons (e.g., internet connection problems, failed to be recorded), the missing data were interpolated with their own previous training data using a forward linear method before statistical analysis. Behavioral data was analyzed using a group (WMT, CON) by time (pretraining “Pre,” post-training “Post”) ANOVA. In addition, to detect if there was difference at baseline between groups, two-tailed independent *t* test was computed. We considered results as statistically significant at $p < .05$. The analysis was conducted using SPSS 19.0 (IBM Corporation, Somers, NY).

Statistical analysis of global CT was conducted using group (WMT, CON) by time (pre, post) ANOVAs for left and right hemispheres separately. For the subcortical volumes of the seven regions, we performed repeated measures ANOVAs of group by time by ROIs for each hemisphere. For all ANOVAs, the threshold of statistically significant results was set at $p < .05$ Bonferroni corrected.

Longitudinal analyses were performed by using longitudinal two stage model with Freesurfer (<http://freesurfer.net/fswiki/LongitudinalTwoStageModel>). First, we reduced the repeated measures to a single statistic for each subject. Here, SPC, a dimensionless measure of change (i.e., the rate of change with respect to the average CT/CV/CSA/LGI) was calculated at each vertex of each subject from both timepoints (Reuter et al., 2012). The formula of SPC calculation is:

$$SPC = 100 * \frac{(V2 - V1)}{(T2 - T1) * 0.5 * (V1 + V2)} = 100 * \frac{\text{rate}}{\text{avg}}$$

where *V1* is the vertex-wise measure (e.g., CT, CV, CSA, and LGI) at baseline (*T1*) and *V2* is the measure at 8-week follow-up (*T2*). The

SPC represents the monthly rate of change with respect to the average CT/CV/CSA/LGI across the two time points. Secondly, within group analysis (within CON group and WMT group separately) as well as group comparisons (comparisons between SPC in WMT group and SPC in CON group) of whole brain SPC in CT, LGI, CV, and CSA were computed with a standard QDEC (general linear model, GLM) in Freesurfer. Comparisons of SPC between groups were conducted to assess group by time interactions. CT, CV, and CSA were smoothed with 10 mm full-width/half-maximum (FWHM) Gaussian smoothing kernels while the LGI was smoothed using 5 mm FWHM Gaussian kernels (Schaer et al., 2012). GLM analyses of each of above measures were performed for left and right hemispheres separately. Monte Carlo simulation (Hagler Jr., Saygin, & Sereno, 2006), a cluster-wise correction, was applied to correct for multiple comparisons for each GLM analysis. Results were considered significant only when the initially obtained clusters ($p < .05$ at vertex-wise level, two-tailed) reached the additional cluster-wise threshold of $p_{\text{cluster}} < .05$ (two-tailed) and 1,000 random permutations.

To explore a potential relationship between training-induced structural changes and training induced verbal WM changes, for each timepoint and each subject of the WMT group we first extracted LGI/CT/CV/CSA values from all clusters showing significant group differences. Then the change scores of Digit Span (post–pre), as well as changes in LGI/CT/CV/CSA (post–pre) were computed. Correlation between behavioral changes and cortical changes in the WMT group was then conducted using partial correlation after controlling for age, gender, and years of education with SPSS 19.0 (IBM Corporation, Somers, NY). We considered results as statistically significant at $p < .05$ Bonferroni corrected.

3 | RESULTS

3.1 | Demographic data

As shown in Table 1, no significant differences in age, gender, and years of education were observed between WMT and CON groups at baseline.

3.2 | WMT and cognitive test

No significant difference in *d'* values was observed between the first four sessions and the last four sessions for verbal *n*-back training or visual *n*-back training in the CON group. The WMT group showed significant improvement in the *d'* values at the end compared to the beginning for both verbal *n*-back training ($t_{[30]} = -6.9$, $p < .0001$) and visual *n*-back training ($t_{[30]} = -6.75$, $p < .0001$). Significant improvement was also found in achieved *n*-back level in both verbal ($t_{[30]} = -7.13$, $p < .0001$) and visual *n*-back training ($t_{[30]} = -6.14$, $p < .0001$; Figure 2).

No significant difference was found between WMT group and CON group at baseline for forward Digit Span Test. A significant

TABLE 1 Demographics of two groups

	WMT (<i>n</i> = 31) Mean ± SD	CON (<i>n</i> = 28) Mean ± SD	<i>p</i> value
Age	55.81 ± 4.23	56.00 ± 4.19	.861
Gender (female/male)	15/16	14/14	.902
YoE	17.03 ± 3.14	16.14 ± 3.06	.276

Note: Gender (categorical data) was tested by using chi-squared tests (χ^2). Abbreviations: CON, active control group; SD, standard deviation; WMT, working memory training; YoE, years of education.

group by time interaction was found ($F_{(1,58)} = 19.3$, $p < .0001$, partial $\eta^2 = 0.26$) indicating a significantly stronger training-related performance improvement in the experimental compared to the control group.

3.3 | Global CT and subcortical volume

As shown in Figure 3 and Figure 4, no significant group by time interaction was observed in mean CT as well as the volume of seven subcortical structures in left or right hemisphere.

3.4 | Vertex-wise cortical measures within each group

The results of training induced structural changes within each group are summarized in Table 2 and Figure 5. For the control group, significant changes (i.e., SPC) were only observed in terms of a greater LGI in left lateral occipital cortex (extending to medial occipital cortex), compared to baseline.

The WMT group showed increased LGI, CT, and CV after training compared to baseline in several areas. The clusters of greater LGI included left inferior parietal lobule, right precuneus and bilateral superior parietal cortex. The clusters of increased CT were located in

the left paracentral lobule and the right precentral gyrus, which were the same regions showing a greater CV. In addition, we observed decreased CSA in bilateral visual cortex, specifically bilateral primary visual cortex and visual association area.

3.5 | Changes of vertex-wise cortical measures between groups

As shown in Table 3 and Figure 6, several group differences of SPC in LGI, CT, CV, and CSA were observed, which were similar to the results within the WMT group. Compared to the CON group, the WMT group showed increased SPC in LGI at bilateral superior parietal cortex and right precentral gyrus. In contrast, one cluster, left cuneus, had smaller SPC in LGI in WMT group than CON group. Greater SPC in CT as well as in CV in the WMT group compared to the CON group was observed in two clusters, namely the left paracentral lobule and the right precentral gyrus. In addition, increased SPC in CV in the WMT group compared to the CON group was found at left precuneus. Compared to the CON group, the WMT group revealed reduced SPC in CSA in one cluster of right lateral occipital cortex.

All the results of SPC in these four vertex-wise cortical metrics (LGI, CT, CV, and CSA) within each group and between groups were corrected using Monte Carlo simulation. On a more conservative threshold (FDR) there were no significant results.

3.6 | Association of behavioral changes and cortical changes

We did not detect any correlations between cortical changes and forward Digit Span change scores after correcting for multiple comparisons. On an uncorrected level, the change in LGI of right superior parietal cortex, however, showed a significant positive correlation with the change in forward Digit Span ($r = .483$, $p = .014$, uncorrected).

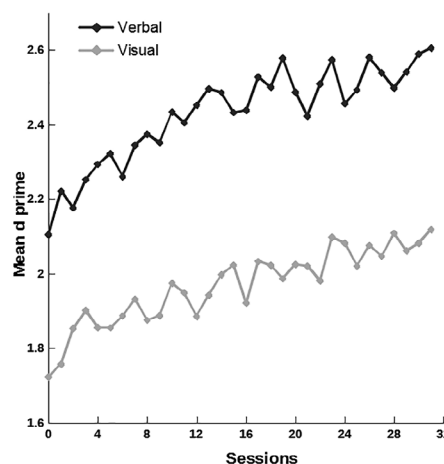
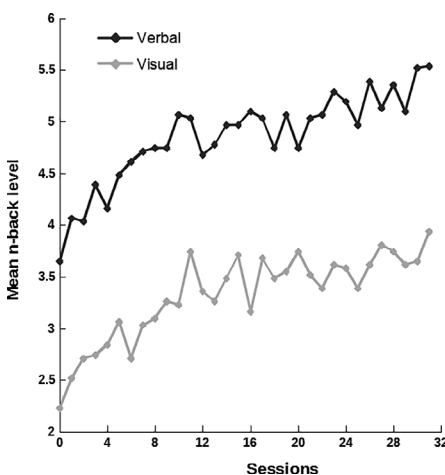


FIGURE 2 Training results of working memory training (WMT) group. Mean *n*-back level per session across 32 sessions for both verbal and visual WMT (left); Mean *d'* values per session across 32 sessions for both verbal and visual WMT (right)

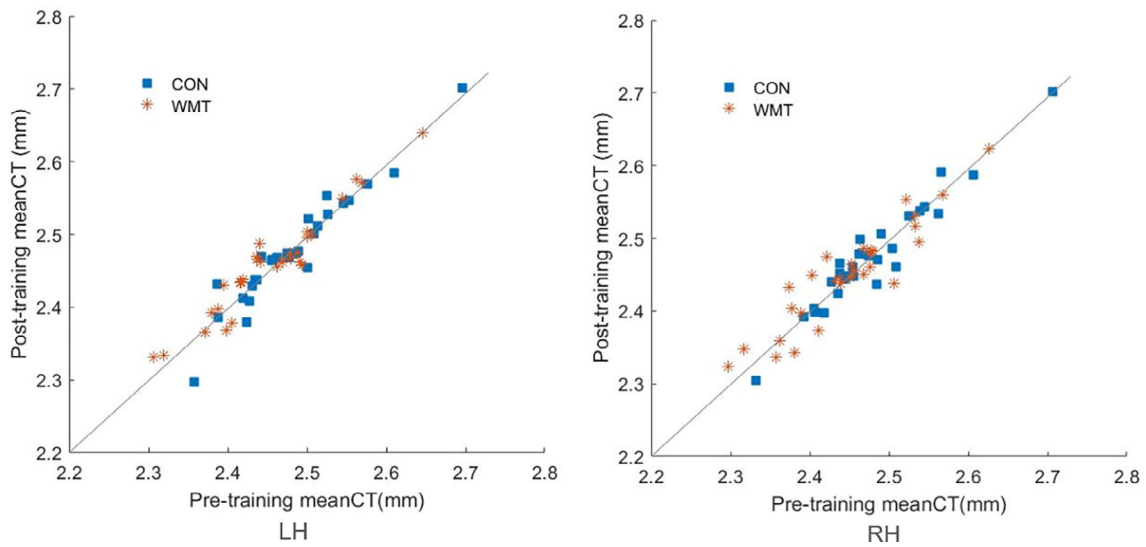


FIGURE 3 Global mean cortical thickness comparison, pre- as well as post-training of each group. CON, active control group; LH, left hemisphere; RH, right hemisphere; WMT, working memory training group

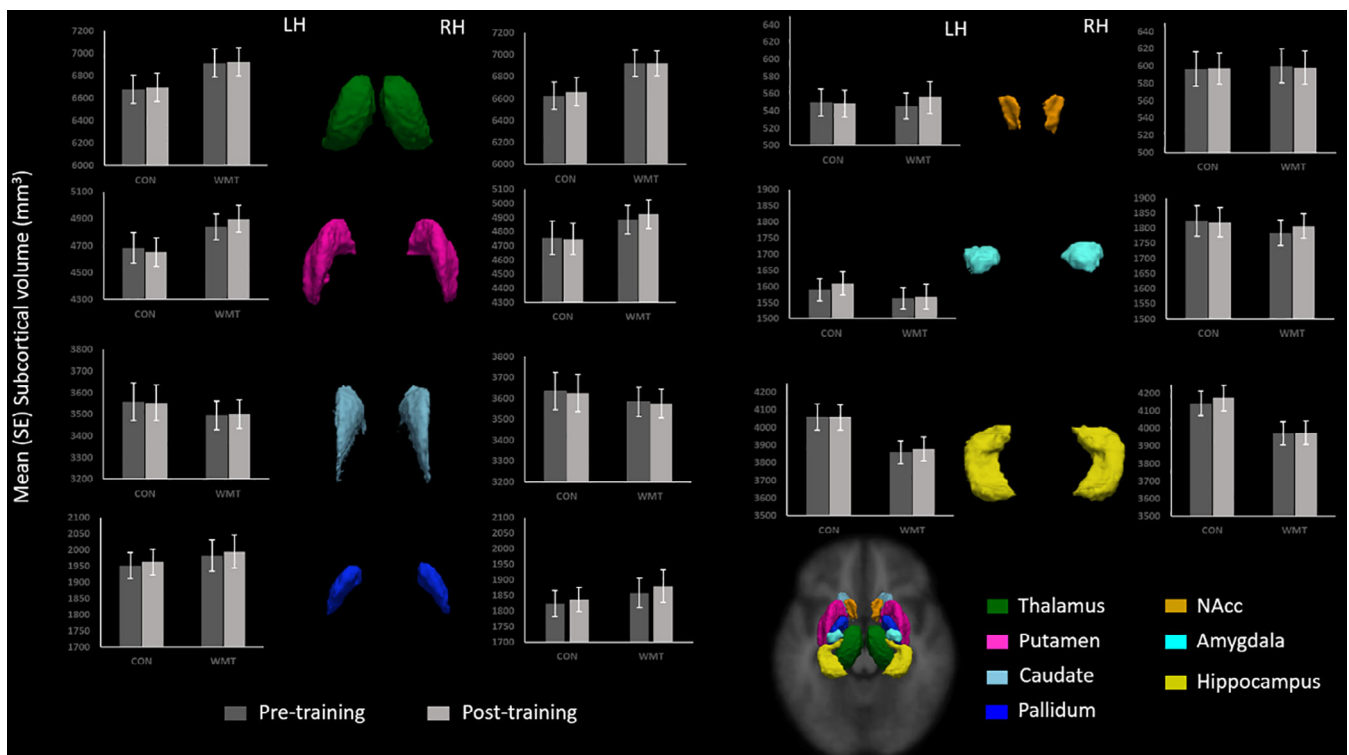


FIGURE 4 Bar graphs of the average subcortical volumes (standard error). CON, active control group; LH, left hemisphere; NAcc, nucleus accumbens; RH, right hemisphere; WMT, working memory training group

4 | DISCUSSION

To our knowledge, this is the first study to investigate the effects of WMT by combining cognitive measures and four different structural measures in a cohort of middle-aged healthy adults.

We found that an 8-week intensive adaptive WMT led to significant changes in gray matter structure in conjunction with significant practice effects (i.e., training performance and *n*-back performance, for more details, refer to Emch, Ripp, et al. (2019) and significant effects on digit span forward performance. Correlations between

TABLE 2 Clusters of cortical changes in each group

Group	Cortical structures	Hemisphere	Max	Size (mm ²)	TalX	TalY	TalZ	No. vertices	Annotation	
WMT	LGI	L	4.36	4,943.93	-19.1	-69.4	39.9	10,432	SPC, IPL	Post
		R	3.11	2,250.48	17.2	-69.4	39.4	9,709.02	SPC, Precuneus	> Baseline
	CT	L	4.84	797.01	-11.7	-36.4	64.8	1959	PL	
		R	4.27	1,124.41	33.9	-19.1	44.4	2,577	PG	
	CV	L	4.98	784.32	-13.3	-36.4	63.7	1950	PL	
		R	4.93	1,100.91	35.9	-18.2	50.8	2,549	PG	
SA	L	-3.79	2,787.33	-22.9	-76.1	-0.8	3,456	mOC	Baseline	
	R	-3.19	1,144.02	28.9	-92.2	-4.6	1,470	IOC	> Post	
	R	-3.43	1,572.58	11.0	-81.4	12.7	2029	mOC		
CON	LGI	L	2.55	2,465.34	-15.7	-92.1	20.6	3,514	IOC, mOC	Post > Baseline

Abbreviations: WMT, Working memory training group; CON, active control group; CT, cortical thickness; CV, cortical volume; IPL, inferior parietal lobule; L, left; LGI, local gyrification index; IOC, lateral occipital cortex; Max, \log_{10} (p value); mOC, medial occipital cortex; PG, precentral gyrus; PL, paracentral lobule; Post, post-training; R, right; SA, surface area; SPC, superior parietal cortex; Tal (X, Y, Z), Talairach (X, Y, Z).

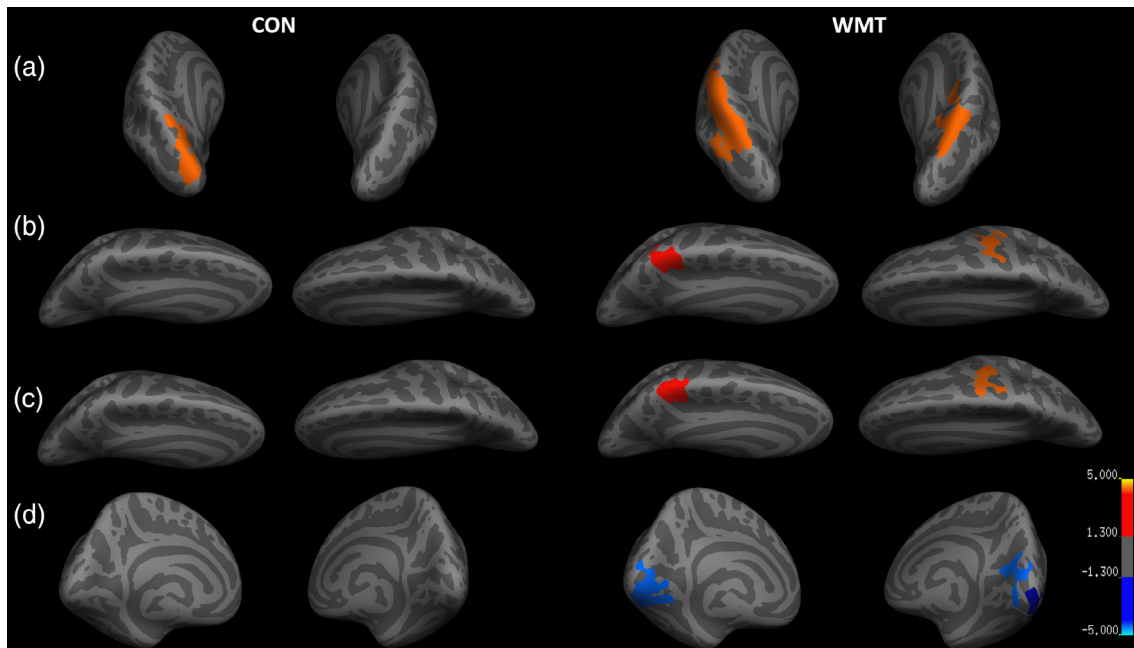


FIGURE 5 Gray matter changes between pretraining (baseline) and post-training in each group. (a) Local gyrification index; (b) Cortical thickness; (c) Cortical volume; (d) Surface area. Colored regions are used to indicate significant changes between pretraining (baseline) and post-training. Red/yellow represents greater values for post-training compared with pretraining, while blue represents greater values at baseline (pretraining) compared with post-training. The value of the color bar is a $\log_{10}(p)$ value. CON, active control group; WMT, working memory training group

cortical changes and digit span performance changes were, however, not detectable.

4.1 | Local gyrification index

As a major finding of the present study, we detected greater cortical folding in bilateral parietal regions (inferior parietal lobule and superior

parietal cortex) in the WMT group after the 8-week adaptive WMT, while in the CON group increased cortical folding was only observed in left lateral occipital cortex (extending to medial occipital cortex) (Figure 5a). Importantly, results of the group comparison (the regions were comparatively smaller, as group by time interaction reflected the training effects with controlling for the nonadaptive training effects from the CON group) were in line with results within each group, except for one additional finding (i.e., greater SPC in right precentral

TABLE 3 Differences in gray matter changes between the groups

Cortical structures	Hemisphere	Max	Size (mm ²)	TalX	TalY	TalZ	No. vertices	Annotation	
LGI	L	3.51	1,044.75	-18.9	-68.4	39.2	2042	SPC	WMT > CON
	L	-3.01	1,372.94	-5.3	-90.8	13.6	1735	Cuneus	CON > WMT
	R	2.97	1,465.38	16.4	-70.3	42.9	2,858	SPC	WMT > CON
	R	2.70	1,334.99	33.0	-18.7	55.2	3,287	PG	WMT > CON
CT	L	3.74	552.86	-11.9	-36.2	66.8	1,344	PL	WMT > CON
	R	4.25	1,083.04	35.1	-23.7	44.0	2,406	PG	WMT > CON
CV	L	3.26	527.40	-10.6	-36.8	62.1	1,262	PL	WMT > CON
	L	2.63	725.55	-5.8	-66.0	42.5	1,421	Precuneus	WMT > CON
	R	4.72	691.73	34.4	-21.4	42.2	1,522	PG	WMT > CON
CSA	R	-2.45	653.52	16.6	-95.7	-2.3	841	IOC	CON > WMT

Abbreviations: CON, active control group; CV, cortical volume; CT, cortical thickness; L, left; LGI, local gyrification index; IOC, lateral occipital cortex; Max, \log_{10} (p value); MTC, middle temporal cortex; PG, precentral gyrus; PL, paracentral lobule; R, right; SA, surface area; SPC, superior parietal cortex; Tal (X, Y, Z), Talairach (X, Y, Z); WMT, working memory training group.

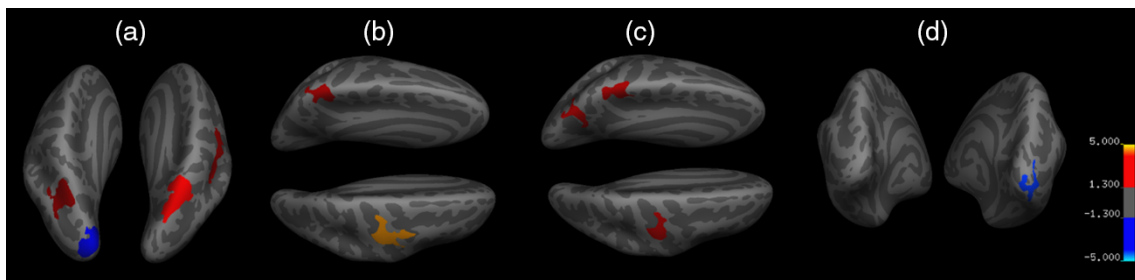


FIGURE 6 Differences of gray matter changes between the groups. (a) Local gyrification index; (b) Cortical thickness; (c) Cortical volume; (d) Surface area. Colored regions are used to indicate significant “group by time interaction.” Red/yellow represents greater values of symmetrized percent change for WMT group compared CON group, while blue represents greater values of symmetrized percent change for CON group compared with WMT group. The value of the color bar is a $\log_{10}(p)$ value). CON, active control group; WMT, working memory training group

gyrus in the WMT group compared to the CON group; Figure 6a). These findings indicate that intensive WM training which requires higher cognitive abilities (e.g., maintenance at increasingly higher n -back levels, continuous updating and processing of information, inhibition of irrelevant information, and decision making; Gajewski, Hanisch, Falkenstein, Thönes, & Wascher, 2018) seems to increase the degree of cortical folding in a region known to be strongly involved in WM processing (i.e., the parietal cortex), whereas intensive training of lower-order cognitive function (i.e., attention, maintenance at a stable low n -back level) leads to an increased cortical folding in a visuo-attentional area (i.e., the occipital cortex). While this is the first study to report training-induced changes in parietal gyrification, previous studies did demonstrate an association between higher degree of cortical folding and better cognitive performance in terms of a positive correlation between degree of parieto-frontal gyrification and WM capacity (Green et al., 2018). The exact mechanisms underlying cortical gyrification remain poorly understood (Gautam, Anstey, Wen, Sachdev, & Cherbuin, 2015; Green et al., 2018), but there is evidence indicating that cortical folding is primarily determined by lifelong experience- or environment-related

factors whereas other cortical metrics (e.g., cerebral volume) are highly determined by genetic variations (Kochunov et al., 2010; Luders et al., 2012; Rogers et al., 2010; White, Andreasen, & Nopoulos, 2002). Thus, cortical folding, the hallmark feature of the cortex surface, reflects the dynamic organization of brain morphometry cortex due to ontogenetic training/learning processes. The gyri bring different regions of gray matter closer together, which might improve the communication efficiency between the respective regions thus allowing for a more efficient cognitive processing. The variability in regional convolution of the cortex may reflect changes of domain-general or domain-specific functions. As mentioned above, in the CON group, participants underwent a very low-load WMT which involved only basic processes of WM (e.g., attention and short-term memory). Occipital regions play a vital role in basic visuo-attentional WM processes by forwarding and transforming information along occipito-parietal and occipito-temporal processing pathways (Ungerleider, Courtney, & Haxby, 1998). Thus, increased gyrification in the occipital cortex might enhance the processing of transforming low-level inputs, thereby improving the efficiency and robustness of low-level related information processing. The training of more

complex WM processes, on the other hand, was associated with reorganization of gyrification in parieto-frontal networks. Parietal regions integrate sensory information, distribute attention, and promote effective encoding, retrieval as well as feedback processes (Bajaj et al., 2018; Gevins & Smith, 2000; Graham et al., 2010). Hence, the increased parieto-frontal gyrification in association with an improvement in WM performance in the WM training group can be taken as evidence for the specific, but restricted cognitive-neurobiological effects of the WM training. That is to say, the detected greater increases of cortical folding in the regions may indicate that, after long-term WMT, participants might be more efficient in integrating multi-modal information (mentioned above) through parieto-frontal network/pathways to make optimal responses. Along this line, the finding of clear-cut training-related alterations restricted to WM-relevant regions fits well with the finding that the training did have effects on WM performance (i.e., digit span forward performance). The specific, but restricted cognitive-neurobiological effect of the WM training was furthermore reflected in a trend (i.e., not corrected for multiple comparisons) significant correlation between changes in right superior parietal cortex LGI and training-related changes in digit span forward performance. This correlation might indicate that the training-induced effects on gyrification, at least in superior parietal regions, are closely associated with cognitive improvements, especially the domains which are same or similar to training tasks. Again, as mentioned at the beginning, this is the first study to report WMT induced effects on brain gyrification, thus further studies are necessary to find out more about the exact mechanisms underlying cortical gyrification and training associated changes of gyrification, as well as the relationship between the degree of gyrification changes and other training induced neural/behavioral changes.

4.2 | CT and CV

CV and CT showed similar changes in the WMT group after the 8-week WMT (Figure 5b,c) and, of note, these results were also detectable when comparing the WMT group to the CON group (Figure 6b,c). Thus, in the WMT group there were significant increases in CT and CV in the left paracentral lobule and the right precentral gyrus and these were also the clusters showing greater increases in the WMT group compared to the CON group. In addition, there was an increased CV in the WMT group compared to the CON group in the left precuneus.

These results have several implications. First, they indicate a close interdependence between the two parameters or, in other terms, they suggest that training-induced changes in CT contribute to changes in CV. This finding is in line with previous evidence showing a close, positive relationship between thickness changes and volume changes (Storsve et al., 2014). The neurobiological mechanisms underlying CT changes are, however, not well understood. CT and CV changes may be related to increased dendritic branching, synaptogenesis, angiogenesis or other processes (Zatorre et al., 2012). Particularly, practice-related gray matter changes may primarily be linked to synaptic

remodeling within specific processing networks (Ilg et al., 2008). Second, the results reflect structural changes restricted to regions that are regarded as relevant for WM processing. Thus, an increased CV in the WMT group compared to the CON group in the left precuneus was found in the present study. In addition, there was an increased CT in the paracentral lobule and precentral gyrus which are important parts of primary motor cortex (PMC). The precuneus has repeatedly been shown to be critically involved in WM processing, especially visuo-spatial WM processing, and its cognitive section holds strong connections with the prefrontal cortex, predominantly prefrontal areas (e.g., Brodmann Area, BA 10 and 46; Cavanna & Trimble, 2006; Lundstrom, Ingvar, & Petersson, 2005; Schott et al., 2019; Silk et al., 2006). The PMC is responsible for planning and movement execution as well as involved in higher order cognition (e.g., attention, learning, movement inhibition; Bhattacharjee et al., 2020; Hoshi & Tanji, 2006; Jeannerod, 2001). Additionally, the balance of excitatory and inhibitory activity in the PMC is closely linked to high load WM-related neural activity (Freeman, Itthipuripat, & Aron, 2016). Previous evidence showed that greater activation in the PMC was associated with faster responding and general intelligence (Bajaj et al., 2018; Emch, von Bastian, et al., 2019). Thus, our findings might suggest that after higher-load WM training, an increased CT in bilateral PMC might contribute to a better balancing of activation and inhibition of specific neurons by reorganizing synapses, thus allowing for an improvement of specific cognitive processes (e.g., faster response times, for more details, refer to Emch, Ripp, et al. (2019); Emch, von Bastian, et al. (2019)).

4.3 | Cortical surface area

Unexpectedly, decreased CSA in bilateral occipital cortex was found in the WMT compared to the CON group after the training (Figures 5d and 6d). CSA is thought to reflect the structural integrity of gray matter (Fischl, Liu, & Dale, 2001; Lemaitre et al., 2012) and to be associated with the number and sizes of cells within radial columns perpendicular to the pial surface. Previous studies demonstrated that CSA is a dynamic process that is related to changes in gyrification (i.e., it increases with gyrification; Green et al., 2018; Wierenga et al., 2014). In the present study, cortical contracting in bilateral occipital cortex in the WMT group might indicate the dynamic process of gyrification of the cortical mantle following training. Specifically, greater cortical folding in bilateral parietal cortex as mentioned above might bring different brain areas closer together and during this dynamic process parts of the occipital cortex might have been stretched and pulled closer to parietal regions resulting in decreased CSA of the occipital cortex. Viewed from this perspective, the findings are plausible and in line with the gyrification findings reported above. To date, only two studies have reported WMT effects on CSA. Roman et al. (2016) found a small surface expansion in right middle temporal cortex in the training group, whereas there were mixed results in the control group (expanding trends in right frontal and anteromedial temporal regions, contracting trends in left temporal-parietal cortex and

right pars opercularis). In contrast, in another recent study no CSA changes after a WM training were observed (Lawlor-Savage et al., 2019). Methodological differences as mentioned above might explain these discrepancies to some degree. As studies on the neuroplastic effects of WMT on CSA are scarce, further studies are necessary to identify the key regions and the degree of CSA changes reflecting the neural mechanisms underlying WMT.

4.4 | Limitations

In the current study a comparatively simple model—longitudinal two stage model, was used as our study was a two-timepoint repeated measures design and all participants had the same number of time points (approximately equally spaced). In the future, a linear mixed effects (LMEs) model (Bernal-Rusiel et al., 2013; which is more complex and currently only implemented in Matlab) would be a more powerful approach, especially for studies with several timepoints or unbalanced data where the LME model can overcome limitations inherent to the longitudinal two stage model. The LME model can handle unequal timing (e.g., significant between-subject variation in between-scan intervals) as well as unbalanced data (e.g., different number of time points across participants and missing data), allowing for participants with even only one single time point to be included in the analyses.

5 | CONCLUSION

In summary, in the present study only practice effects were found, no near or far transfer effects could be detected. Thus, we challenge the proposition that WMT effects can be transferred to other cognitive domains. In addition, present findings suggest that cortical folding might represent the most relevant and most plastic characteristic of WM and learning and might reflect WM training effects to a greater extent than the other metrics (i.e., CV, CT, and CSA). Structural training-induced changes in WM-related regions, especially parietal regions (i.e., inferior parietal lobule and superior parietal cortex), seem to constitute a macrostructural indicator of an improvement in WM performance and, at the same time, provide a better brain processing environment for higher load WM tasks. Further studies are needed to develop cognitive interventions allowing for improvements in multiple cognitive domains which might then go along with structural alterations in more extended regions or networks.

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CONFLICT OF INTEREST

The authors report no competing interests.

DATA AVAILABILITY STATEMENT

The codes and commands for imaging processing are offered at <https://surfer.nmr.mgh.harvard.edu>. The data that support the findings of this study are available from the corresponding author on reasonable request. In this study, all participants have signed an informed consent form approved by the local ethic committee stating that their data will only be made accessible to a third person for the purpose of clinical examination.

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