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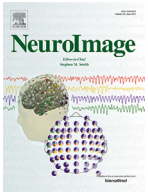

Neuronal efficiency following n-back training task is accompanied by a higher cerebral glucose metabolism

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ABSTRACT

Recent functional magnetic resonance imaging (fMRI) studies revealed lower neural activation during processing of an n-back task following working memory training, indicating a training-related increase in neural efficiency. In the present study, we asked if the training induced regional neural activation is accompanied by changes in glucose consumption. An active control and an experimental group of healthy middle-aged volunteers conducted 32 sessions of visual and verbal n-back trainings over 8 weeks. We analyzed data of 52 subjects (25 experimental and 27 control group) for practice effects underlying verbal working memory task and 50 subjects (24 experimental and 26 control group) for practice effects underlying visual WM task. The samples of these two tasks were nearly identical (data of 47 subjects were available for both verbal and visual tasks). Both groups completed neuroimaging sessions at a hybrid PET/MR system before and after training. Each session included criterion task fMRI and resting state positron emission tomography with FDG (FDG-PET). As reported previously, lower neural activation following n-back training was found in regions of the fronto-parieto-cerebellar circuitry during a verbal n-back task. Notably, these changes co-occurred spatially with a higher relative FDG-uptake. Decreased neural activation within regions of the fronto-parietal network during visual n-back task did not show co-occurring changes in relative FDG-uptake. There was no direct association between neuroimaging and behavioral measures, which could be due to the inter-subjects' variability in reaching capacity limits. Our findings provide new details for working memory training induced neural efficiency on a molecular level by integrating FDG-PET and fMRI measures.

1. Introduction

Cognitive training programs aiming to enhance cognitive abilities and ameliorating cognitive deficits became a hot topic in the field of cognitive neuroscience over the last years. Specifically, working memory training (WMT) became increasingly popular and a core feature in many cognitive training programs. As a non-pharmacological intervention, WMT has been widely used in both clinical and non-clinical populations (Bigorra et al., 2016; Heinzel et al., 2016; Hill et al., 2017; Huntley et al., 2017; Pang et al., 2021; Roberts et al., 2016). The reason for the popularity lies in the fact that WM is linked to attention and executive functioning skills (Diamond, 2013; Kane et al., 2007), which seem to be crucial for and involved in many cognitive task processing strategies (Diamond, 2013). Meta-analyses report consistent and strong practice effects, that is cognitive improvements in the WMT task (i.e. criterion task), due to WMT (Sala et al., 2019; Soveri et al., 2017). However, the neural biological substrate mediating the change on the behavioral level is not yet well understood.

A meta-analysis by Salmi et al. (2018) reported functional brain changes due to WMT within different networks such as the dorsal attention and salience network, sensory areas, and striatum. The authors reported WMT associated in- and decreased neural activation based on criterion task fMRI data (i.e., the trained task). It is assumed that both in- and decreased neural activities are results of neural plasticity. While decreases in neural activation have been interpreted as an increased neural efficiency, increases in neural activation have been regarded as a selective increase of neuronal involvement in the task (for a review see Constantinidis and Klingberg 2016). Based on previous WMT studies using the n-back task as the training paradigm it seems that

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training induced decreased activation in WM related regions is present under low and medium demands (e.g., up to 3-back) (Aguirre et al., 2019; Clark et al., 2017; Heinzel et al., 2016; Miró-Padilla et al., 2019; Schneiders et al., 2012, 2011; Schweizer et al., 2013), while increased activations become manifest at higher loads (e.g., 4-back and 5-back) (Buschkuehl et al., 2014; Schweizer et al., 2013). Our group reported significantly decreased neural activation in WM characteristic regions in the experimental group compared to an active control group based on verbal WM task fMRI data (i.e., when comparing activation of 3-back vs. 0-back) (Emch et al., 2019). However, as also acknowledged in the review by Constantinidis and Klingberg (2016), the blood oxygenation level dependent (BOLD) signal is only an indirect measure of neural activity based on the neurovascular coupling. Thus, the BOLD signal reflects an estimate of neural activity which is dependent on a complex interplay between cerebral vascular activity, blood flow, blood volume and neural/synaptic activity. Consequently, it is desirable to investigate if these WMT induced activation changes can be described with additional neuroimaging parameters helping to contribute understanding the physiological changes. As such, positron emission tomography (PET) with [18F] fluorodeoxyglucose (FDG-PET) has proven immensely useful for the study of neuroenergetics in the living human brain, both in clinical and research settings (Bohnen, 2012; Riedl, 2016). FDG-PET is supposed to estimate neural or synaptic activity more directly than BOLD by capturing glucose consumption in terms of neurometabolic coupling. It has been shown that task induced changes in regional glucose metabolism can be captured with a novel continued infusion paradigm of FDG-PET (Hahn et al., 2016; Jamadar et al., 2019) which led to the identification of neural correlates of a visuo-spatial task (Hahn et al., 2020). Along the same line, our group was able to capture neural correlates of a visual and verbal WM task (i.e., 2-back and 3-back) in terms of increased uptake of FDG using a standard clinical FDG-PET imaging protocol with single bolus injection (Ripp et al., 2021). These observations have proven that FGD-PET allows to identify neural correlates underlying a cognitive, and more specifically, a WM task. However, as to our knowledge the direct relationship between practice related changes in glucose metabolism, practice related changes in BOLD signal and practice related improvements in behavioral performance has not been investigated up to now.

Against this background, an active control and an experimental group of middle-aged healthy volunteers underwent FDG-PET and fMRI imaging before and after an 8-week visual and verbal WMT period. Using this design, we intended to investigate if WMT induced regional neural activation changes underlying task fMRI co-occur with changes in glucose consumption.

2. Methods and materials

2.1. Subjects

The study was approved by the Federal Office for Radiation Protection and the local ethics review board. Participants were recruited via advertisements in the internet and on hospital bulletin boards. The subjects were right-handed, in the age range 50–65 years, free of cognitive deficits, neurological or psychiatric diseases. Further inclusion criteria were absence of contraindications for MRI and no brain anomalies on structural MRI images. All participants provided written, informed consent. They were randomly assigned single-blinded to an experimental (EXP) or an active control (CON) group. Participants of both groups underwent neuroimaging before and after an 8-week visual and verbal WMT period. The criteria for the interval between scans pre- and after-training was: maximum 9 days (i.e., the interval between first scan and start of training as well as the interval between the end of training and second scan was maximum 9 days). Among initially recruited subjects six were excluded: two due to image artefacts from large falx ossifications on MRI, one due to a failure to follow the training program; imaging data of two subjects were saved incompletely; one participant dropped out for private reasons after the first neuroimaging session. After pre-processing (see *Imaging pre-processing* section), 6 participants (i.e., 2 due to excessive head movement, 1 due to poor normalization, and data from 2 participants were removed because of performance outliers) were excluded for the final verbal WM analysis while 8 participants (i.e., 4 due to excessive head movement, 1 due to poor normalization, and 3 performance outliers) were excluded for the final visual WM analysis. Performance outliers were detected by a combination of statistical (values are 3 or more standard deviations from the mean) and graphic (boxplot) methods, followed by investigating the nature of the outliers (e.g., the accuracy values of within-scanner performance were extremely low because of missing responses). Thus, participants with performance outliers were excluded from further analysis. Finally, data of fifty-five participants were available for further analyses. Specifically, 47 out of 55 participants were available for both visual and verbal analysis, meaning the samples of these two tasks were basically identical. Of the eight remaining participants, three of them were available only for visual analysis, and five of them only for verbal analysis. Therefore, 52 participants (EXP = 25, CON = 27) were included in the final analysis for practice effects underlying verbal WM task and 50 participants (EXP = 24, CON = 26) were included in final analysis for practice effects underlying visual WM task (Table 1).

2.2. Working memory training procedure

The detailed description of WMT procedure can be found in previous study (Emch et al., 2019). Briefly, all participants underwent supervised training on a personal computer at home using a visual and verbal *n*-back task over 8 weeks (~20 min per session). The EXP group performed an adaptive *n*-back paradigm for visual and verbal tasks. The *n*-back level was adapted to the participant's performance. Specifically, the *n*-back level increased for a subsequent block if more than 90% of correct responses were given, and it decreased if less than 80% of correct responses were given. Otherwise, the *n*-back level remained the same. The adaptive level of *n* ranged from 1-back to a maximum difficulty level of 9-back. The CON group performed non-adaptive low level visual and verbal *n*-back training (i.e., 1-back verbal task and X-back visual task), using equivalent stimuli. The order of tasks trained (visual or verbal *n*-back) was counterbalanced between subjects in each group. The participants were instructed to complete four training sessions per week and one training session per day. After each training session, logfiles were automatically uploaded to the Millisecond Software website (https://www.millisecond.com/). Based on information saved in the logfiles, a weekly training progress report was sent via email to all participants.

2.3. Task-fMRI paradigm

In the scanner, subjects performed a visual and a verbal n-back task (Fig. 1). Methodological details are described in Emch et al. (2019). Briefly, both visual and verbal WM tasks included seven blocks of control condition (i.e., x-back) and seven blocks of the task condition (i.e., 3-back for verbal and 2-back for visual WM task given the differing degrees of familiarity of the stimulus material). Each condition lasted 45 s, including 5 s of an instruction to the following condition, 5 s of fixation cross presentation, and 35 s of stimulus presentation, resulting in a total duration of 10.5 min for each fMRI n-back task. In the n-back task, any letter, or shape could be a target, in the X-back condition only the capital letter "X" was a target for the verbal WM task and one specific predefined shape was a target for visual WM task. The order of presentation with regard to verbal and visual n-back task was counterbalanced between the first and the second session. The participants did not receive performance feedback after each block as in comparison for the training sessions.

Table 1
Demographics-verbal and visual working memory task cohort.

Cohort		N	Gender M/F	*p* value	Age M(SD)	*p* value
Verbal	Experimental	25	12/13	0.78*	55.52 (4.14)	0.95†
Cohort	Active control	27	13/14		55.63 (4.27)	
Visual	Experimental	24	13/11	0.98*	55.75 (4.28)	0.96†
Cohort	Active control	26	14/12		55.69 (4.27)	

M, male; F, female; M (SD), mean (standard deviation); * Chi-Square Test
† t-test

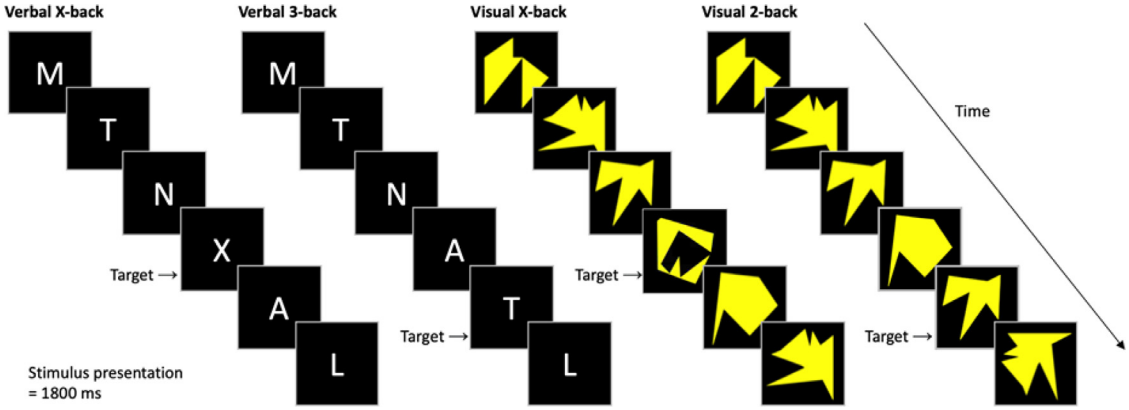

Fig. 1. Schematic overview of N-back paradigm during fMRI.

2.4. Imaging data acquisition and preprocessing

2.4.1. Imaging data acquisition

Imaging data were acquired 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. The subjects were instructed to fast for six hours prior to each of two PET/MR sessions. Around 100 MBq FDG were injected intravenously to participants sitting in a quiet, dimly lit room, after confirming normal blood glucose levels. The following MR sequences were acquired over the first 30 min of imaging (i.e., 30–60 min p.i.): localizer, μ-map, structural T1-weighted, FLAIR, echo-planar imaging (EPI) 2D diffusion for diffusion tensor imaging (DTI) and EPI-PACE (Echo-Planar Imaging - Prospective Acquisition Correction) sequence for resting state fMRI.

Task-fMRI was acquired 60 to 90 min p.i. using a gradient-echo T2$*$-weighted EPI sequence with the following parameters: 237 volumes; 40 slices; TR = 2700 ms; TE = 30 ms; flip angle = 90°; voxel size = 3.0 × 3.0 × 3.0 mm^3; slice thickness = 3 mm; 0.6 mm gap; FOV = 192 × 192 mm^2; interleaved acquisition. The WM paradigm was presented using Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA, United States). The subjects' responses were collected via fORP 932 subject response package (Cambridge Research Systems). The participants were able to see the task through a mirror fixed to the head coil which reflected the MRI-compatible screen. Participants were positioned supinely in the scanner and held the button-box in their right hand and the emergency button in their left hand.

PET data were acquired for 60 min in list mode with a craniocaudal scan direction and a z-axis distance of 26 cm. For each subject we reconstructed a single frame FDG-PET summation image for 30–60 min p.i. PET image reconstruction was performed offline using Siemens e7 Tools (Siemens Molecular Imaging, Knoxville, USA). Ordered subsets expectation maximization (OSEM) algorithm with 3 iterations of 24 subsets with a 5 mm Gaussian filter, to eliminate the high frequency noise, was used. The resulting PET images had a matrix dimensions of 344 × 344 with 127 sagittal slices with a reconstructed voxel size of 1.04 × 1.04 × 2.03 mm^3. Tissue segmentation based magnetic resonance attenuation correction (MRAC) was performed using an ultra-short time of echo (UTE) μ-map which was acquired with the following parameters: 192 sagittal slices; voxel size = 1.56 × 1.56 × 1.56 mm^3; matrix size = 192 × 192, and FOV = 300 mm x 300 mm.

A high-resolution T1-weighted magnetization prepared – rapid gradient echo (MP-RAGE) anatomical sequence was acquired with the following parameters: 160 slices; TR = 2300 ms; TE = 2.98 ms; flip angle = 9°; voxel size = 1.0 × 1.0 × 1.0 mm^3; slice thickness = 1 mm; no gap; FOV = 256 × 256 mm^2; interleaved acquisition. The same imaging protocol was used in both sessions (i.e., before and after WM training period). The presence of significant microangiopathic lesions and incidental findings were excluded upon visual assessment of structural MRI images.

2.4.2. Imaging preprocessing

All DICOM neuroimaging data was converted to 3D-NIFTI volumes using the dcm2niix tool (https://github.com/neurolabusc/dcm2niix), expect for fMRI data, for which we used dcm2nii. Task fMRI and FDG-PET data were pre-processed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and MATLAB v2017b (The MathWorks Inc., Natick, Massachusetts, USA).

The fMRI data pre-processing steps included head motion correction, co-registration of the subjects' T1-weighted image to the functional images, segmentation of transformed T1 images, spatial normalization to MNI space, and smoothing with an 8 mm isotropic Gaussian filter. Specifically, for motion correction, the images were realigned and resliced to fit the mean functional image. Excessive head motion was defined as translation >= 3 mm or rotation >= 3° (Johnstone et al., 2006; Landini et al., 2018).

PET images were co-registered to structural MPRAGE image (T1) and subsequently spatially normalized into MNI space using the forward deformation field resulting from segmentation of T1, followed by smoothing with an 8 mm isotropic Gaussian filter.

2.5. Statistical analyses

2.5.1. Working memory training

Working memory training improvements were assessed by means of *d* prime (d') and achieved n-back level. *d*' takes the range for both *hits*

and *misses* into account by calculating the Z transformed *hit rate* minus *false-alarm rate* ($d\prime = ZHit - ZFA$) (Haatveit et al., 2010; Meule, 2017). Higher values of *d*' represent better performance whereas lower values of *d*' values represent worse performance. For both groups a t-test between the average *d*' value of the first and the last four training sessions was calculated. For the experimental group an additional t-test between the average n-back level of the first and the last four training sessions was computed. This test was not applied to the control group as their n-back level stayed steady across the 32 training sessions.

2.5.2. Task fMRI paradigm: behavioral performance

Behavioral performance of fMRI tasks was assessed by computing a repeated-measures analyses of variance (ANOVA) with group (EXP, CON) as between-subjects factor, session (T1, T2) as within-subject factor, and d' values of each condition (i.e., 3-back or X-back for verbal WM task, 2-back or X-back for visual WM task) as dependent variable. Post hoc t-test were applied to assess within group changes.

2.5.3. Neural correlates of practice effects – fMRI

In the single subject level analysis, a general linear model (GLM) was conducted for verbal and visual task separately. The BOLD signal was estimated by convolving the stimulation periods (task blocks) with the canonical haemodynamic response function (HRF). The six motion parameters were included as covariates of no interest to model the head motion correlated effects. A high-pass filter (220 s) was used to eliminate low-frequency components. The contrasts of interest were 3-back > X-back for verbal task paradigm and 2-back > X-back for visual task paradigm. They were modeled for each participant to capture the brain regions activated during higher-level working memory processing.

Also, the second level analyses were performed for verbal and visual task paradigm separately. To investigate the training induced effects, a longitudinal analysis was carried out by using the SPM12-implemented factorial design with group (CON, EXP) as between-subjects factor and session (T1, T2) as within-subject factor. Statistical significance was assumed at $p < 0.05$ false-discovery rate (FDR) corrected at a voxel level. To avoid exploration of spurious results in addition to the FDR threshold we used a cluster extent threshold of 50 voxels.

Finally, the resulting clusters from the significant interaction between group and session were converted into binary masks for the subsequent FDG-PET analysis (Fig. S1 Supplementary Material).

2.5.4. Neural correlates of practice effects – FDG-PET

To test the hypothesis if neural correlates of practice effects based on task fMRI data co-occur with a change in FDG-uptake we extracted the mean FDG-uptake out of each verbal and visual binary fMRI mask (see above). We normalized the masks' FDG-uptake by global mean FDG-uptake retrieved with the function *spm_global* from SPM. In-house written MATLAB code was used for extracting relative FDG (rFDG) uptake values. Relative FDG-uptake values were analyzed with a two-way mixed-effects analysis of variance (ANOVA) for repeated measures with the between-subjects factor group (CON, EXP) and the within-subjects factor session (T1, T2) using SPSS 26 (IBM Corporation, Somers, NY). We considered results as statistically significant at $p < 0.05$ Bonferroni corrected for multiple comparisons (i.e., 2). Post-hoc two-sample t-test was applied to test for significant baseline differences in rFDG-uptake between CON T1 and EXP T1 using the function *ttest2* from MATLAB v2017b. Post-hoc paired t-tests were applied to test for significant difference in rFDG-uptake between CON T1 and CON T2 and EXP T1 and EXP T2 using the function *ttest* from MATLAB v2017b. Assumptions of normality were tested with a Jarque-Bera test using the function *jbtest* from MATLAB v2017b. We considered results as statistically significant at $p < 0.05$.

2.5.5. Neuroimaging-behavior correlation

To investigate the relationship between neuroimaging parameters and behavioral measures in regards to practice effects in the experimental group we conducted a correlation analysis for each neuroimaging modality and WM task performance.

For fMRI we correlated the change in haemodynamic response of the significant clusters by means of parameter estimates resulting from the GLM with the change in *d*' of the respective WM task across the subjects.

For FDG-PET we correlated the change in rFDG-uptake within each binary fMRI mask with the change in *d*' of the respective WM task across all subjects. For all brain-behavior correlations we defined the change in neuroimaging and behavioral measures as the difference between timepoint 2 min timepoint 1 (T2 - T1). Pearson correlations were computed SPSS 26 (IBM Corporation, Somers, NY. A $p < 0.05$ Bonferroni - corrected for multiple comparisons per neuroimaging modality (i.e., 2) was set as the significance threshold.

2.5.6. Brain-brain correlation

To investigate the relationship between neuroimaging parameters from both modalities in regards to practice effects in the experimental group we conducted a correlation analysis. We correlated the change in haemodynamic response by means of parameter estimates (see above) against the change in rFDG-uptake for each verbal and visual fMRI mask. Pearson correlations were computed with SPSS 26 (IBM Corporation, Somers, NY. A $p < 0.05$ Bonferroni - corrected for multiple comparisons (i.e., 2) was set as the significance threshold.

3. Results

3.1. Demographics

Demographic characteristics of the participants for both verbal and visual WM task sample are summarized in Table 1. There was no significant difference for age or gender between the experimental and the active control groups in the verbal or visual WM task cohort. Thus, no correction for these variables was applied (Spector and Brannick, 2011).

3.2. Working memory training

The experimental group showed significant practice effects (*d*') and improvements in n-back level in both verbal and visual *n*-back training (Table 2 and Fig. 2). In the active control group, *d*' values did not significantly differ between the beginning and the end of verbal or visual *n*-back training (Table 2).

3.3. Task fMRI paradigm: behavioral performance

The results of WM performance are shown in Fig. 3. In the univariate analysis of variance (ANOVA) for d' verbal WM task, main effects of session ($F_{(1,50)} = 10.86$, $p < 0.0001$) and group ($F_{(1,50)} = 40.59$, $p < 0.0001$), as well as a significant *group* × *session* interaction ($F_{(1,50)} = 18.84$, $p < 0.0001$) were found. Similarly, repeated ANOVA on d' visual WM task showed main effects of both session ($F_{(1,48)} = 75.07$, $p < 0.0001$) and group ($F_{(1,48)} = 4.06$, $p = 0.05$), as well as significant interaction between group and session ($F_{(1,48)} = 20.64$, $p < 0.0001$). Post *hoc* t-tests revealed a significant improvement in d' values for both the verbal ($T_{(1,24)} = -6.91$, $p < 0.0001$) and visual ($T_{(1,23)} = -8.13$, $p < 0.0001$) WM tasks in the experimental group. In contrast, in control group, the performance of neither verbal ($T_{(1,26)} = -1.59$, $p < 0.125$) WM task nor visual ($T_{(1,25)} = -1.44$, $p = 0.162$) WM task improved significantly.

3.4. Neural correlates of practice effects-Task fMRI

Significant group by session interactions were observed for both verbal WM (Fig. 4A and Table 3) and visual WM (Fig. 4B and Table 4). Specifically, for verbal WM (3-back > X-back), brain regions showed a significant interaction (EXP (T1 > T2) > CON (T1 > T2)) mainly in bilateral posterior cerebellum, angular/supramarginal gyrus, prefrontal

Table 2
Practice effects-results of working memory training data.

Parameters	EXP T1M (SD)	T2M (SD)	T-test *T*	*p*	CON T1M (SD)	T2M (SD)	T-test *T*	*p*
verbal *d'*	2.14(.16)	2.51(.34)	-6.3	<0.0001	4.65(.25)	4.70(.20)	-1.14	.265
visual *d'*	1.81(.14)	2.09(.29)	-5.64	<0.0001	4.72(.23)	4.79(.22)	-1.36	.187
Verbal n-back level	3.98(.62)	5.31(1.26)	-6.3	<0.0001	N/A	N/A	N/A	N/A
Visual n-back level	2.51(.62)	3.73(1.24)	-5.41	<0.0001	N/A	N/A	N/A	N/A

EXP, experimental group; CON, active control group; M (SD), mean (standard deviation)

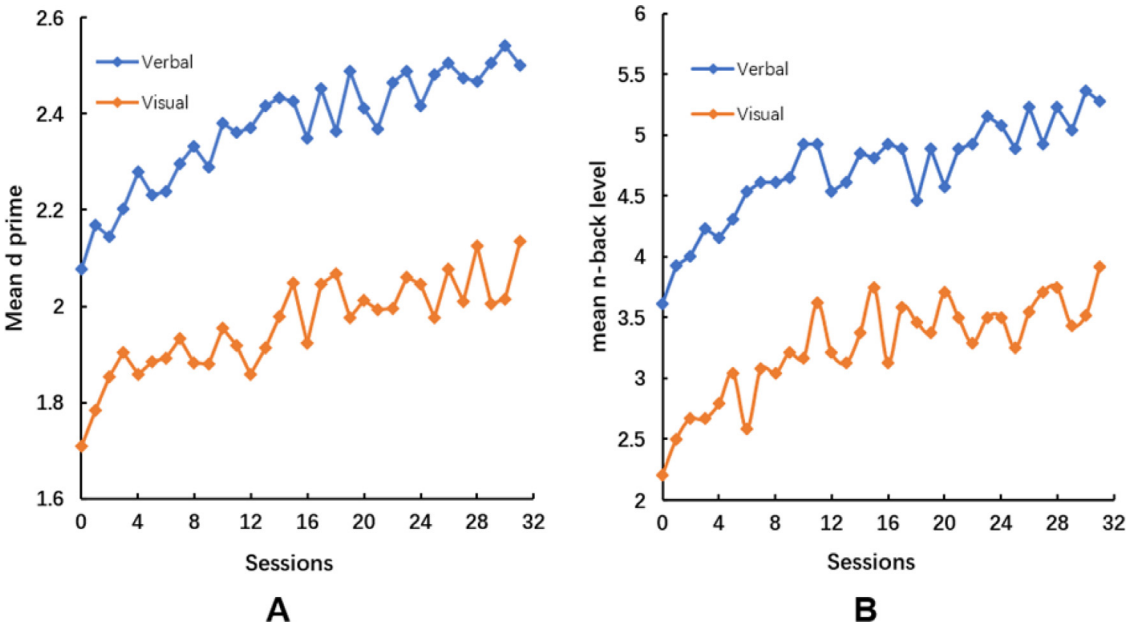

Fig. 2. *Training results for the experimental group*. (A) d prime mean values per session across 32 training sessions for both verbal and visual training tasks (B) n-back level mean values per session across 32 training sessions for both verbal and visual training tasks.

Table 3
Brain regions of brain activation in verbal fMRI task showing significant group × session interaction.

Region	BA	Hemisphere	Cluster size	MNI Coordinates x	y	z	*Z*
Cerebellum (PL)		L	1128	-28	-74	-34	5.37
Cerebellum (PL)		R	304	18	-78	-26	3.83
AG/SPL	39/7	L	890	-52	-50	36	4.50
AG/SG/SPL	39/40/7	R	3443	48	-50	20	4.77
dACC/dlPFC	32/9	R	194	8	44	4	3.58
Dorsal PCC	31	L	84	-10	-42	42	3.55
Ventral PCC	23	R	75	28	-56	6	4.35
Occipital cortex	17	L	101	-18	-72	4	4.28
Hippocampus		R	56	20	-22	-6	3.96
MTG	21	L	76	-58	-36	-6	3.85
dlPFC	9	R	62	16	48	30	3.50

PL, posterior lobe; BA, brodmann area; L, left; R, right; AG, angular gyrus; SG, supramarginal gyrus; dACC, dorsal anterior cingulate cortex; dlPFC, dorsal lateral prefrontal cortex; PCC, posterior cingulate cortex; MTG, medial temporal gyrus; SPL, superior parietal lobule; MNI, Montreal Neurological Institute; results were $p < 0.05$ FDR voxel-corrected with a cluster extent of k > 50.

Table 4
Brain regions of brain activation in visual fMRI task showing significant group × session interaction.

Region	BA	Hemisphere	Cluster size	MNI Coordinates x	y	z	*Z*
dlPFC/antPFC	9/10	Bilateral	1705	8	48	34	4.55
PCC/Precuneus	23/31/7	Bilateral	245	-6	-50	24	4.16
PCC/Precuneus	31/7	L	78	-16	-44	0	4.07
AG/SG	39/40	R	208	54	-52	32	4.1
Fusiform gyrus (extending to Parahippocampus)	37/36	L	50	-30	-38	-18	4.24

BA, brodmann area; L, left; R, right; dlPFC, dorsal lateral prefrontal cortex; antPFC, anterior prefrontal cortex; PCC, posterior cingulate cortex; AG, angular gyrus; SG, supramarginal gyrus; MNI, Montreal Neurological Institute; results were $p < 0.05$ FDR voxel-corrected with a cluster extent of $k > 50$.

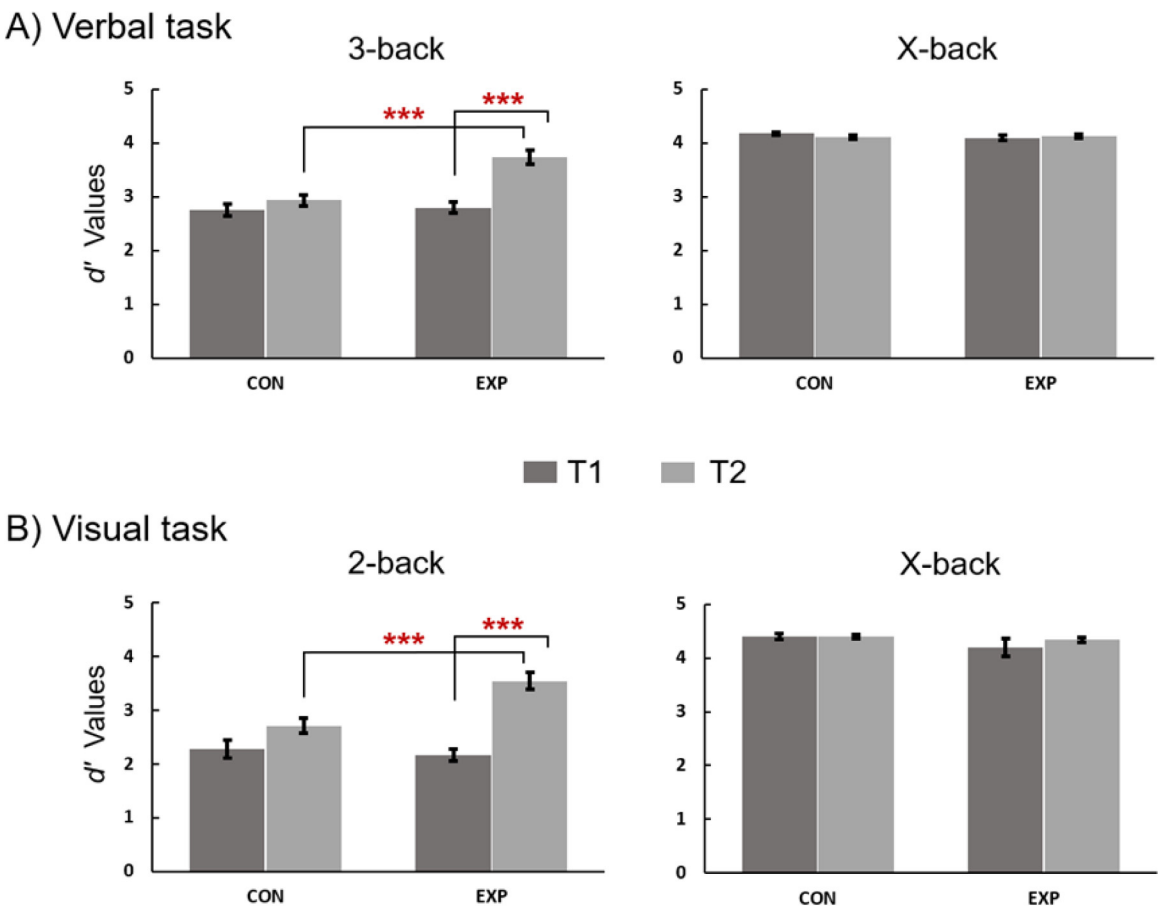

Fig. 3. *Results of fMRI task performance*. Data show the mean values ± SEM. EXP, experimental group; CON, active control group; T1, pre-training; T2, post-training; ***, $p < 0.0001$.

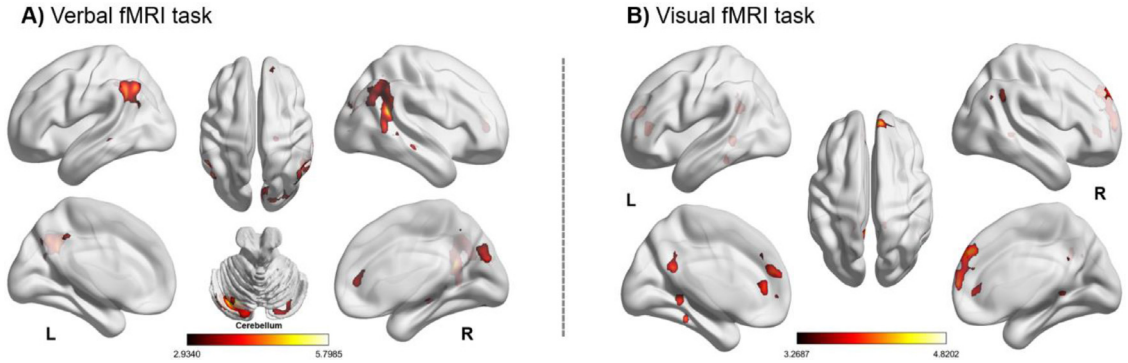

Fig. 4. *Results of training-related activation changes in verbal and visual tasks*. Contrast: experimental group (T1>T2) > control group (T1>T2); L, left; R, right; results were $p < .05$ FDR voxel-corrected with a cluster extent of $k > 50$.

cortex, posterior cingulate cortex, left occipital cortex and middle temporal gyrus. For visual WM (2-back > X-back), brain regions such as bilateral prefrontal cortex, posterior cingulate cortex, right angular gyrus, and left fusiform which extended to para-hippocampus showed a significant group by session interaction (EXP (T1 > T2) > CON (T1 > T2)). Post-hoc analyses revealed that, following WMT, the neural activation in the respective brain regions significantly decreased in the EXP group for both verbal and visual WM tasks (Fig. 5A and B), thus corroborating the results of ANOVA. In contrast, neither the verbal nor the visual WM tasks demonstrated significant changes in the CON group for either of the contrasts (i.e., CON T1 > CON T2, or CON T1 < CON T2). Results were $p < 0.05$ FDR voxel-corrected with a cluster extent threshold of $k = 50$ voxels.

3.5. Neural correlates of practice effects-FDG-PET

For rFDG-uptake extracted from the verbal fMRI mask, the repeated measures ANOVA showed no significant main effect of session (Wilks Lambda = 0.975; $F_{(1,50)} = 1.28$; $p = 0.263$). However, a significant interaction between group and session was observed (Wilks Lambda = 0.875; $F_{(1,50)} = 7.16$; $p = 0.010$). Post-hoc t-tests revealed a significant increase

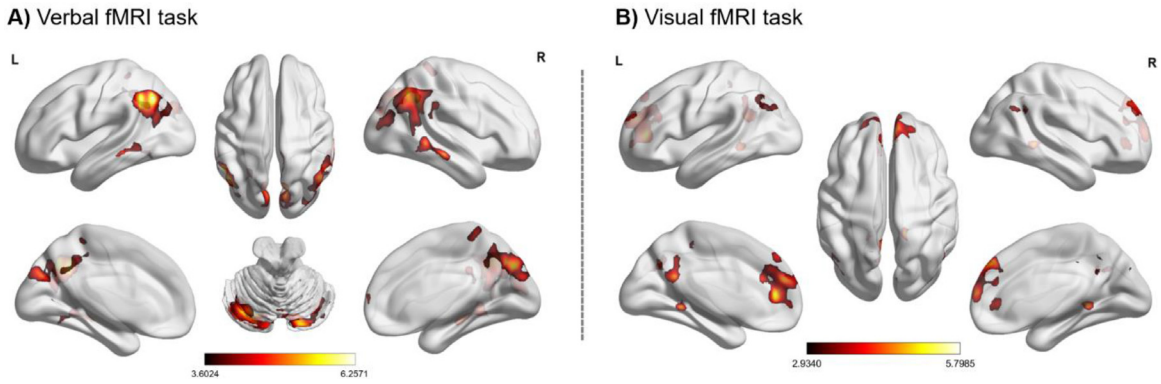

Fig. 5. *Results of post-hoc analyses within EXP group for verbal and visual tasks*. Contrast: EXP group T1> EXP group T2; L, left; R, right; results were $p < .05$ FDR voxel-corrected with a cluster extent of $k > 50$.

Table 5
Posthoc tests rFDG-uptake – verbal fMRI mask.

Between group	T1		T-test		T2		T-test	
	EXPM (SD)	CONM (SD)	*T*	*p*	EXPM (SD)	CONM (SD)	*T*	*P*
rFDG-uptake	1.91 (0.07)	1.93 (0.08)	-1.16	0.25	1.93 (0.07)	1.92 (0.08)	1.13	0.97
Within Group								
	EXP		**T-test**		**CON**		**T-test**	
	T1M (SD)	**T2M (SD)**	***T***	***p***	**T1M (SD)**	**T2M (SD)**	***T***	***P***
rFDG-uptake	1.91 (0.07)	1.93 (0.07)	-2.58	**0.02**	1.93 (0.08)	1.92 (0.08)	1.13	0.27

M (SD), mean (standard deviation).

in rFDG-uptake from T1 to T2 in the experimental group, whereby all other comparisons showed no significant changes (Table 5).

For rFDG-uptake extracted from the visual fMRI mask, no main effect of session (Wilks Lambda = 0.942; $F_{(1,48)} = 2.947$; $p = 0.092$) and no significant interaction between group and session was observed (Wilks Lambda = 0.972; $F_{(1,48)} = 1.362$; $p = 0.249$).

3.6. Brain-behavior correlation

No significant correlation between change in neuroimaging parameters and behavioral measures (i.e., *d'*) was observed (Fig. S1).

3.7. Brain-brain correlation

No significant correlation between change in haemodynamic response and relative FDG-uptake within verbal or visual fMRI masks were observed (Fig. S2).

4. Discussion

In this study we examined if neural activation changes based on criterion task fMRI data due to WMT in healthy middle-aged participants is accompanied by a change in glucose consumption based on FDG-PET data.

Briefly, we found significant training-induced improvements in behavioral performance (i.e., trained verbal and visual n-back tasks, as well as verbal and visual fMRI WM performance), accompanied by a significant decrease in brain activation in WM-related areas in frontoparietal regions. Moreover, the reduction in neural activation induced by WMT during verbal fMRI WM performance but not visual fMRI WM performance co-occurred with an increase in glucose consumption.

First of all, results on the behavioral level corroborated the efficacy of the WM training. There was a significant improvement in both visual and verbal fMRI WM performance in the experimental group after the WM training. The improvement in the fMRI WM performance in the experimental group went in line with a significant training performance improvement in this group. These findings indicate that the training was an effective approach to increase WM capacities. As such they corroborate earlier results such as those by Tusch et al. (2016) who reported an improved WM performance in elderly subjects as a consequence of an adaptive computerized WM training, those by Li et al. (2008) who found improved WM performance after a 45-day non-adaptive spatial n-back training in both younger and older adults, those by Dahlin et al. (2008b) who reported a significantly improved WM performance as a consequence of a 5-week computer-based WM updating training, likewise in both younger and older adults or those by Brehmer et al. (2012) showing results in a similar direction.

On the neural level, consistent with previous studies, we observed that WMT resulted in decreased neural activation in WM-associated areas in frontoparietal regions during the performance of both verbal and visual tasks. Specifically, during verbal fMRI performance, compared to the CON group, the EXP group showed a significantly decreased neural activation mainly in a fronto-parieto-cerebellar circuitry (e.g., bilateral posterior cerebellum, posterior cingulate cortex, angular/supramarginal gyrus, right superior parietal lobule, prefrontal cortex) after 8-week WMT, which is consistent with previous studies (Aguirre et al., 2019; Clark et al., 2017; Emch et al., 2019; Miro-Padilla et al., 2019; Schweizer et al., 2013; Thompson et al., 2016). Similarly, the clusters of training-induced decreased brain activation during the performance of the visual task were mainly located in frontoparietal areas, including bilateral prefrontal cortex, precuneus/PCC, right angular/supramarginal gyri, and left fusiform (extending into Parahippocampus) (Hempel et al., 2004; Schneiders et al., 2011; Schneiders et al., 2012). Taken together, results at the behavioral and brain activation levels suggest that WMT is associated with improved behavioral performance and decreased brain activation, indicating better neural efficiency (Buschkuehl et al., 2014; Miro-Padilla et al., 2019). Interestingly, we also detected decreased training-related activation in the occipital cortex during the verbal task. In previous studies, only very few studies have reported n-back training-induced increased (Dahlin et al., 2008a) or decreased (Schweizer et al., 2013) activation in this region. Heterogeneous approaches such as training program, duration, location, in-

tensity, control groups (active or passive control), and populations may explain these discrepancies. Further studies are necessary to find out whether activation changes in occipital cortex are associated with neural mechanisms underlying WMT.

The foremost finding of the present study is that the training-induced decreased neural activation underlying verbal WM co-occurs with an increase in glucose consumption based on FDG-PET. These findings indicate that the directionality of change between both neuroimaging modalities is inverse. Namely, regions showing a WMT induced decrease in BOLD signal exhibited an increase in rFDG-uptake. Due to the fact that the BOLD signal is an indirect measure of neural activation which is dependent on cerebral blood flow, volume and cerebral metabolic rate of oxygen extraction the driving factor for the change in BOLD signal cannot clearly be determined based on the present data. On the other hand, an increase in regional rFDG-uptake can be interpreted as an increase in neural and/or synaptic glucose consumption.

For the visual WM task, however, no such observation was made. Several possible reasons could play a role here. First, we see that the spatial extent, as well as partially the magnitude in change (i.e., Z-values) in neural activation based on BOLD data is larger for the verbal WM task. Assuming an, albeit inverse, association between the two parameters there is good reason to assume that potential co-occurring changes in rFDG-uptake within the visual fMRI mask were also of lesser extent, leading to non-significant changes. Second, while FDG-PET data in the present study reflects resting state related cerebral glucose consumption, BOLD data in the present study reflects verbal or visual WM task related neural activation. Thus, we are not able to distinguish between visual and verbal WMT specific effects in FDG-uptake. Hence, changes in rFDG-uptake within regions showing significantly decreased neural activity as captured by verbal WM task fMRI, could also potentially stem from visual WM training. However, even though resting-state FDG-PET was used, we still observed changes in rFDG-uptake within significant task fMRI clusters. We would expect a stronger change in FDG-uptake in task fFDG-PET after WM training. As this is the first study to investigate the relationship between training induced changes in FDG uptake and BOLD signals, further examinations are required in the future.

While we see rFDG-uptake changes within brain regions showing changes in BOLD signal, we did not observe a direct correlation between those two neuroimaging measures. There are several potential explanations for the lack of correlation. First, it is unclear if the changes in BOLD signal and FDG-uptake are linear. In a previous cross-sectional study, Marchitelli et al. (2018) investigated the relationship between glucose consumption and neural activity during resting state. They found that FDG-uptake correlated with resting-state fMRI metrics of intrinsic activity and functional connectivity, which indicates that cerebral glucose metabolism is closely integrated with different levels of brain functional organization (e.g., neural activity and interneural communication). However, it is important to note that the different brain states underling fMRI (i.e., task processing) and FDG-PET (i.e., resting state) in the present study potentially contribute to the lack of a significant correlation. Also, fMRI and PET underlie different time scales. While PET represents a summed image of FDG-uptake over the chosen timeframe, fMRI represents ongoing neural activity based on the BOLD signal sampled at the rate of the time of repetition (i.e., 2700 ms in the present study). Thus, it is unclear which effects the different time scales have on the relationship between those distinct measures of neural activity. Second, a recent study on brain-behavior relationships discussed the existence of a high degree of inter-subjects' variability in reaching WM capacity limits (Lamichhane et al., 2020). Additionally, region specific WM load-activity relationships, in U-, inverted U and linear shapes have been shown (Lamichhane et al., 2020). Thus, it is possible that the subject pool discussed in the present study is too variable in regards to WM capacity and that the averaged activation over the brain masks cancelled out region specific WM load-activity relationships. Third, we defined and analyzed the change in BOLD as resulting parameter estimates (i.e., betas) from the GLM fitting the haemodynamic response function against the task function. Thus, the parameter estimates are just an estimate of the mathematical equation and do not represent the magnitude of haemodynamic response per se. Future studies should investigate if other measures of task fMRI or a combination of different methods represent a more appropriate or direct measure of neural activity that might then be found to correlate with regional FDG-uptake or other neuroimaging parameters. Present results, on the other hand, seem to indicate that task fMRI and FDG-PET as implemented in the current form capture separate neuronal processes that, nevertheless, might both per se reflect WMT induced changes in cerebral metabolism.

Similarly, we showed a lack of correlation between change in neuroimaging parameters and change in cognitive performance. From a neuroscientific point of view, this is puzzling as it stands that neural correlates of practice effects drive the change on the behavioral level. But, as mentioned above, non-linearity of the data could lead to non-significant relationships.

On a functional level, we can only speculate that WM training leads potentially only to low changes in glucose consumption in the resting brain but probably to higher changes in glucose consumption when conducting the criterion task. However, further research is needed here (see below). Thus, we speculate that WMT elicits functional changes which are restricted to WM task processing (i.e., neural correlates of practice effects). These functional changes are comprised by a simultaneous increase in glucose consumption and a decrease in neural activation, leading to an increase in overall neural efficiency during task processing. However, we acknowledge that our FDG-PET imaging protocol is not ideal to fully explore this relationship as it lacks a constant infusion of FDG limiting us to resting state related FDG-uptake data. Also, we note that we did not assess cerebral metabolic rate of glucose (CMRGlu) which specifically allows the absolute quantification of glucose consumption. This limits us to relative FDG-uptake measures resulting from contrasting cluster wise vs. whole brain FDG-uptake. This means we cannot fully explore where the change in rFDG-uptake is originating from (i.e., a change in whole brain, or cluster wise FDG-uptake). Future studies should implement a continues FDG-infusion PET protocol with blood sampling to allow for the modeling of regional CMRGlu during WM task processing.

5. Limitation

As a limitation to the study it should be mentioned that we were not able to control whether each training session was indeed performed by the subject intended to perform the training since - due to practical reasons as well due to well-known disadvantages going along with personal supervision (such as, e.g., observer effects) - we decided for a training taking place at home.

6. Conclusion

In summary, consistent with the literature, WMT leads to behavioral improvements and reduced neural activation for both visual and verbal criterion tasks. Additionally, we show that neural correlates of verbal WMT practice effects are characterized by a reduced neural activation within regions of the frontoparietal network measured with task fMRI and a simultaneous increase in rFDG-uptake. The results indicate that neural efficiency induced by training/learning is achieved by a simultaneous change in regional activation and glucose consumption. This study provides new details for neural substrates underlying training/learning. An interesting focus of future studies could be to integrate the combined information (e.g., the rates of glucose metabolic and cerebral oxygen consumption, as well as quantification of cerebral blood flow) by using simultaneous PET/fMRI to investigate neural mechanisms underlying training/learning.

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Data and code availability

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.

No new code was developed for generating the results. All results were obtained by functions belonging to publicly available software. The used software and/or functions are stated at appropriate location in the manuscript in the Methods section.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Credit authorship contribution statement

Isabelle Ripp: Conceptualization, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Qiong Wu:** Conceptualization, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Lara Wallenwein:** Formal analysis, Writing – review & editing. **Mónica Emch:** Investigation, Writing – review & editing. **Igor Yakushev:** Supervision, Writing – review & editing, Funding acquisition. **Kathrin Koch:** Conceptualization, Methodology, Supervision, Writing – review & editing, Funding acquisition.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2022.119095.

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