Title: A randomized, double blind study of computerized cognitive training in combination with transcranial direct current stimulation (tDCS) in stroke patients – utility of fMRI as marker for training outcome

Authors: Knut K. Kolskår[a,b,c,*], Geneviève Richard[a,b,c], Dag Alnæs[a], Erlend S.Dørum[a,b,c], Anne-Marthe Sanders[a,b,c], Kristine M. Ulrichsen[a,b,c,], Jennifer Monereo Sánchez[a], Hege Ihle-Hansen[d], Jan E. Nordvik[e], Lars T. Westlye[a,c,*]

[a] NORMENT, Division of Mental Health and Addiction, Oslo University Hospital & Institute of Clinical Medicine, University of Oslo, Norway

[b] Sunnaas Rehabilitation Hospital HT, Nesodden, Norway

[c] Department of Psychology, University of Oslo, Norway

[d] Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway

[e] Catosenteret Rehabilitation Center, Son, Norway

* Corresponding authors: Knut K. Kolskår (kolskaar@gmail.com, +47 995 97 425) & Lars T. Westlye (l.t.westlye@psykologi.uio.no), Department of Psychology, University of Oslo, Pb. 1094, Blindern, 0317 OSLO, Norway, phone: +47 22845000, Fax: +47 22845001

Keywords: stroke, rehabilitation, fMRI, cognitive training, tDCS.

Abstract

Computerized cognitive training (CCT) combined with transcranial direct current stimulation (tDCS) has showed some promise in alleviating cognitive impairments in patients with brain disorders, but the robustness and possible mechanisms are unclear. In this prospective double-blind randomized clinical trial we investigated the feasibility and effectiveness of combining CCT and tDCS, and tested the predictive value of and training-related changes in fMRI-based brain activation during attentive performance (multiple object tracking) obtained before, during and after the three-weeks intervention. Patients were randomized to one of two groups, receiving CCT and either (1) tDCS targeting left dorsolateral prefrontal cortex (1 mA), or (2) sham tDCS, with 40s active stimulation (1 mA) before fade out of the current. 77 patients were enrolled in the study, 54 completed the cognitive training, and 51 completed all training and MRI sessions. We found significant improvement in performance across all trained tasks, but no additional gain of tDCS. fMRI-based brain activation showed high reliability, and higher cognitive performance was associated with increased tracking-related activation in the anterior cingulate after compared to before the intervention. We found no significant associations between cognitive gain and brain activation measured before training or in the difference in activation after intervention. Combined, these results show significant training effects on cognitive tasks in stroke survivors, with no clear evidence of additional gain of concurrent tDCS.

Introduction

While stroke mortality has decreased during the last decades in western countries, it remains a leading cause of disabilities (Feigin et al., 2017), and many stroke survivors experience persistent cognitive sequelae. Indeed, prevalence of neurocognitive disorders in post stroke survivors have been reported to as high as 54% (Barbay et al., 2018), and may increase risk of dementia (Pendlebury, 2012). Reduced working memory capacity is among the most common impairments (Teasell, 1992; Zinn et al., 2007), with high prevalence at the chronic stage (Mahon et al., 2017; Schaapsmeerders et al., 2013), and potentially large impact on daily functioning (Synhaeve et al., 2014). Stroke lesions influences brain activation patterns (Altamura et al., 2009), and working memory deficits have been linked to aberrant activation during task engagement (Ziemus et al., 2007).

Computerized cognitive training (CCT) has shown some promise in augmenting cognitive rehabilitation. A recent meta-analysis revealed small but significant improvements on cognitive functioning in response to CCT in healthy participants (Au et al., 2015). Similar findings have been reported in patients with Parkinson's disease (Leung et al., 2015), mild cognitive impairment (Maffei et al., 2017), brain injury (Weicker et al., 2016), and stroke (De Luca et al., 2018b; Peers et al., 2018), as well as schizophrenia (Prikken et al., 2018) and major depression (Motter et al., 2016). However, the underlying mechanisms remain elusive.

Non-invasive electrical stimulation of the brain has been suggested to augment training benefits (Kang et al., 2015; Marquez et al., 2015). Indeed, evidence suggests amplified motor recovery post-stroke, when physical therapy is paired with transcranial direct current stimulation (tDCS) (Kang et al., 2015), and the beneficial effects have been suggested to generalize to a cognitive rehabilitation context (Andrews et al., 2011; Fregni et al., 2005; Lawrence et al., 2018). Despite some positive findings, the overall effectiveness of tDCS has been questioned (Medina and Cason, 2017). Also, the potential mechanisms, if any, are

unclear, yet enhancing neuronal excitability by lowering the membrane-potential has been suggested as one of the candidate means (Giordano et al., 2017).

Functional MRI has become an increasingly used non-invasive brain imaging method linking behavior to brain activation patterns. Studies investigating alterations in brain activation in response to CCT have reported mixed results. In healthy controls, training gains have been associated with decreased activity in medial and dorsal frontal areas, including anterior cingulate (Heinzel et al., 2016; Miró-Padilla et al., 2018; Motes et al., 2018), with increased efficiency reflected in lowered activity as a suggested cognitive mechanism (Constantinidis and Klingberg, 2016). For patient cohorts the current evidence is sparser, but increased activity in frontal and parietal areas in response to cognitive training has been reported in patients with schizophrenia (Haut et al., 2010; Ramsay and MacDonald, 2015; Subramaniam et al., 2014). In stroke patients, CCT has been associated with increased functional connectivity (FC) between hippocampus, frontal and parietal areas, which was associated with improved cognitive performance (Lin et al., 2014; Yang et al., 2014).

Despite some promising findings the effects of CCT (Buitenweg et al., 2018; De Luca et al., 2018a; Melby-Lervåg and Hulme, 2013; Melby-Lervåg et al., 2016) and tDCS (Dedoncker et al., 2016; Hill et al., 2016) are still unclear. More knowledge about the origins of individual differences in training gains is key to evaluate the value of these interventions.

To this end, we investigated training-related effects of a commonly used working memory computerized training program in combination with tDCS, and tested the predictive value and sensitivity of fMRI-based brain activation as a marker for training-related gain in task performance. Specifically, we estimated activation-patterns during a multiple object tracking task (Alnæs et al., 2014; Dørum et al., 2016; Pylyshyn and Storm, 1988) at baseline, before initiating training (on average 4 weeks after baseline measure), and after a three-week intervention. To assess specific associations with tDCS and following a double-blind design, in addition to CCT each participant was pseudo-randomized into two groups: 50% (n=27)

receiving active tDCS-stimulation and 50% (n=27) receiving sham stimulation, directed towards the left dorsolateral prefrontal cortex.

We tested the following hypotheses: (1) Cognitive training enhances performance on trained tasks, and level of improvement is affected by tDCS stimulation protocol. (2) fMRI-based brain activation patterns prior to training are predictive of training gain. (3) Individual differences in task improvement are reflected in differential patterns of brain activation after the three-weeks intervention, in particular involving frontal and parietal brain regions.

Methods

Sample and exclusion criteria

Figure 1 depicts the study recruitment pipeline. Participants were recruited from two major hospitals located in Oslo, Norway (Stroke unit at Oslo University hospital, and Geriatric department at Diakonhjemmet Hospital, Oslo, Norway). Hospital staff identified suitable participants, in a chronic phase, without other severe neurological, developmental, or psychiatric comorbidity. Approximately 900 invitations were sent out, and 250 responded; among those, 77 patients were eligible for participation and were initially included in the study (Ulrichsen et al., 2019). 19 participants withdrew from the study prior to (n=13) or during (n=6) the cognitive training due to the labor-intensity of the intervention. Four participants were excluded due to medical reasons violating the inclusion criteria. In total, 54 participants completed the cognitive training program. One participant had corrupted behavioral data from fMRI assessment, and was excluded from all MRI analysis. For MRI assessment 3, one participant had poor alignment to the MNI-template, and one participant was not able to complete the task, yielding a total of 53 baseline and 51 with full MRI at all timepoints.

The study was approved by the Regional Committee for Medical and Health Research Ethics South-East Norway, and all participants provided written consent.

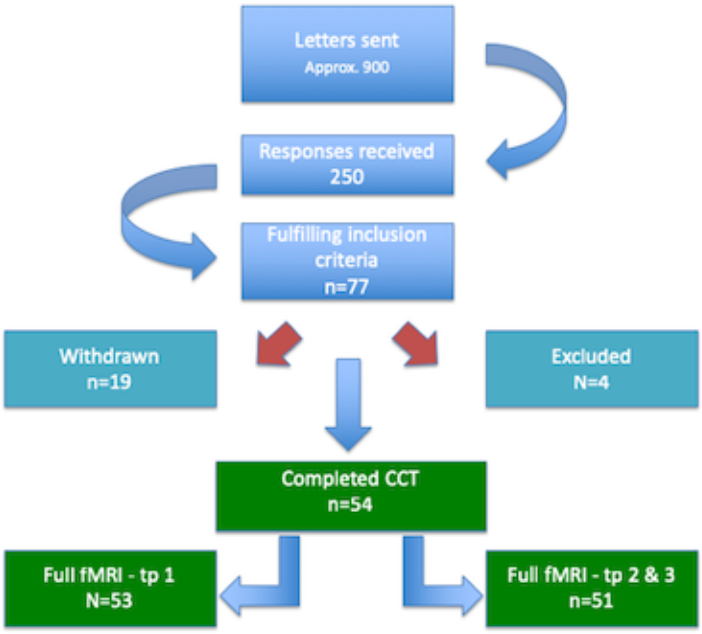

Figure 1. Flowchart displaying inclusion pipeline

Patient characteristics and lesion demarcation

Sample characteristics for the participants completing the intervention (n=54) are described in Table 1, including NIHSS (Goldstein et al., 1989), TOAST (Adams et al., 1993), MMSE (Strobel and Engedal, 2008) and IQ derived from WASI (Ørbeck and Sundet, 2007).

For each participant, lesion demarcation was performed by a trained assistant, utilizing the semi-automated toolbox clusterize, implemented for SPM8 (Clas et al., 2012; de Haan et al., 2015), and guided by radiological descriptions. Figure 2 displays a probabilistic lesion map across participants. Supplementary Figure 1 provides an overview of individual lesions.

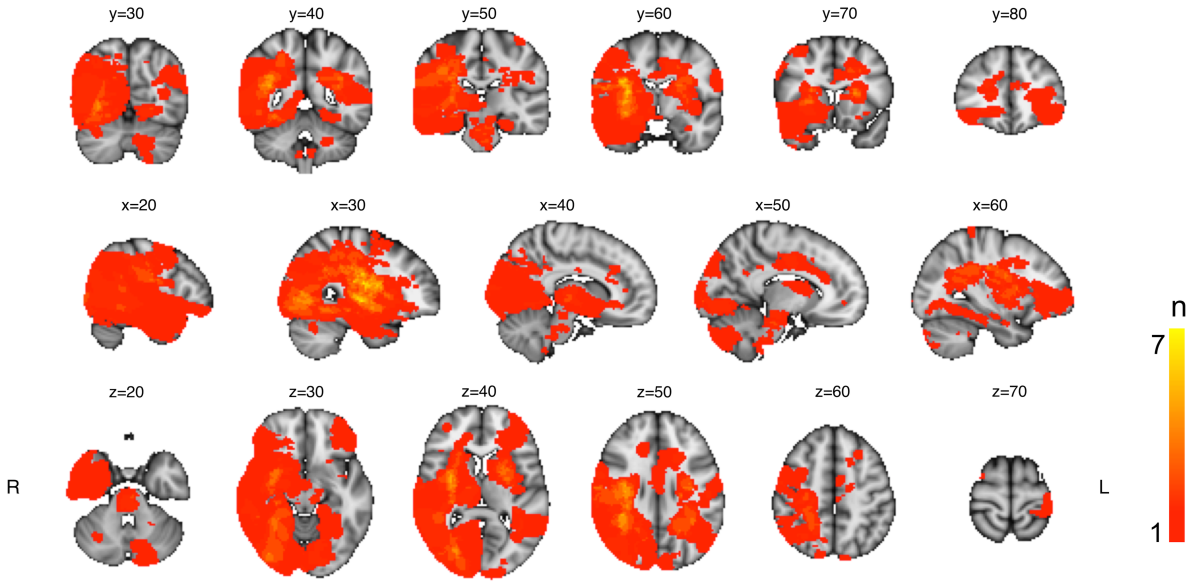

Figure 2. Heatmap displaying lesion overlap across included participants.

	Mean	sd	Min	Max
Participant descriptives (current)				
Age at inclusion	69.13	7.374	47	81
Males (%)	74.07	-		
Time between stroke and inclusion (months)	25.74	9.17	6	45
Self-reported education in years	14.39	3.71	9	30
MMSE at inclusion	27.98	1.855	22	30
IQ	110.45	16.906	66	136
Days between inclusion and training	33.78	12.986	19	74
Days between MRI assessment pre/post training	31.72	6.257	19	49
Clinical variables during hospitalization				
NIHSS at discharge	1.33	1.53	0	7
TOAST classification	Large vessel disease Small vessel disease Cardioembolic disease Other		n=20 n=18 n=6 n=10	

Table 1. Sample characteristics

Cognitive training

The patients performed a computerized working memory training program (Cogmed QM, Cogmed Systems AB, Stockholm, Sweden), comprising 12 auditory-verbal and visual-spatial working memory tasks. The participants completed 17 training sessions over the course of three weeks. The two first sessions were used to adjust the task difficulty to each individual's

level of performance and were excluded from further analysis. We included eight tasks with more than three training sessions in the analysis.

tDCS

Participants were randomly assigned to either active or sham condition, using codes provided by the manufacturer and implemented by an in-house Matlab script, pseudo-randomizing participants while maintaining balance in groups of 20. tDCS stimulation was applied at six occasions for each participant, with a minimum of 48 hours between stimulations, aiming at an average of two stimulations per week. Stimulation current was 1000 μA, stimulation time was 20 minutes for the active group with a ramp-up time of 120 seconds and fade-out time of 30s. The sham stimulation consisted of rampup followed by 40 seconds of active stimulation and then fade-out, following factory settings. Stimulation was delivered via a battery-driven direct current stimulator (neuroConn DC stimulator plus, Germany), through 5 x 7 cm rubber pads, yielding a 28.57 μA/cm2 current density at skin surface. Impedance threshold at start-up of stimulation was < 20 kΩ, and was regulated by the device with an absolute threshold at 40 kΩ for automatically terminating stimulation. The pads were covered with high-conductive gel (Abralyt HiCl, Falk Minow Services Herrsching, Germany) to enhance conductance.

Electrode location was determined by following the 10-20 system, where the anodal electrode was located at F3 corresponding to left DLPFC and cathodal at O2 corresponding to right occipital/cerebellum, and fixated with rubber bands.

fMRI task

Participants performed a blocked version of the multiple object-tracking task (MOT) (Pylyshyn and Storm, 1988), as previously described in detail (Alnæs et al., 2015b). Briefly, the participants were presented ten identical circles on a grey background. All objects were initially blue, before zero (passive viewing), one (load 1) or two (load 2) of the objects turned

red for 2.5 seconds, designating them as targets. After all objects had returned to blue, the objects started moving randomly around the screen for 12 seconds. After the 12 second tracking period, the objects became stationary, one of the objects turned green, and the participants were instructed to respond “yes” or “no” to whether or not the green probe had been designated as a target in that trial. If the trial was a passive viewing trial, the participant was instructed to keep fixation on the screen. The task consisted in total of 24 semi-randomized trials ensuring the same condition was not repeated consecutively.

MRI acquisition

MRI data was acquired with a 3T GE 750 Discovery MRI scanner (32-channel head coil) located at Oslo University Hospital. T1-weighted images was acquired using a 3D IR-prepared FSPGR (BRAVO) with the following parameters: scan time: 4:43 minutes and included 188 sagittal slices, repetition time (TR): 8.16 ms, echo time: 3.18 ms, flip angle: 12º, voxel size: 1 × 1 × 1 mm, field of view: 256 x 256 mm,

Functional MRI sequences was acquired with a BOLD-sensitive gradient echo planar sequence, with TR of 2.25 s, TE 30 ms, field of view 256 x 256 mm, slice thickness 3 mm with 0.5 mm gap acquired ascending interleaved, 90º flip angle, with R/L orientation. The initial first five volumes were removed before analysis.

fMRI data processing

fMRI data was processed using FMRI Expert Analysis Tool (FEAT) Version 6.00, from FMRIB's Software Library (FSL; Jenkinson et al., 2012; Smith et al., 2004), and included the following steps: correction for motion using MCFLIRT (Jenkinson et al., 2002), linear trend removal and high-pass filtering (0.01 Hz), removal of non-brain tissue using BET (Smith, 2002), spatial smoothing with a Gaussian kernel of full width at half maximum (FWHM) of 6 mm (SUSAN ; Smith and Brady, 1997), and linear registration using FLIRT (Jenkinson and

Smith, 2001) to Montreal Neurological Institute (MNI) 152 standard space using the T1-weighted scan as an intermediate. In the same manner, normalization parameters were estimated for each participants T2-weighted image, and applied to the demarked lesion.

Statistical analysis

Cogmed main effects of time: To investigate the trajectory of Cogmed performance across participants and time points, linear mixed effects (lme) models were estimated for each test, using the lme function from the nlme-package (Pinheiro et al., 2017) in R. Task performance was entered as dependent variable, with training session as independent variable, and age, sex, tDCS-group, educational level in years (self-reported) interaction between training session and tDCS as fixed factors, and participant as random factor.

Cogmed individual trajectories: To quantify individual trajectories in Cogmed performance across the training-period, we estimated for each test and each participant a linear model with performance as dependent variable and session number as independent variable, yielding a beta-estimate (slope) for each test for each participant reflecting changes in performance over time. As a measure of overall performance for each participant, we used the average task performance across sessions for each test for each participant. To investigate task homogeneity in beta-estimates and average performance we performed multivariate outlier detection with the aq.plot function in the mvoutliers package in R (P. Filzmoser and Gschwandtner, 2018), with an alpha of 0.001 and 90% of the sample to estimate the minimum covariance determinant. Two subtests ("hidden objects" and "Digits") were found to have a high number of outliers compared to the other subtests, and were excluded from further analysis (See Supplementary Figure 2 for details). For transparency, subsequent analyses were performed both with and without the outliers included.

To derive a common score for average Cogmed performance and gain, we performed a principal component analysis (PCA) on beta-estimates and average performance,

respectively. All scores were zero-centered and standardized prior to running the PCA. We used the first factor from the beta PCA as a *Cogmed change score*, and the first factor from the average performance PCA as a *Cogmed average performance score (*see Supplementary Figure 3 for scree-plot derived from the PCA performed on both with and without the excluded tasks*)*.

To assess the association between Cogmed scores and lesion severity, we estimated linear models for both Cogmed change and average performance scores, using lesion volume, number of lesions and their interaction as explanatory variables. Models were estimated using the lm function in the stats package in R (Team, 2013).

fMRI analysis: First-level GLMs for each participant and scanning session were estimated using FEAT (Woolrich et al., 2001), including regressors for passive viewing, load 1, load 2, responses, as well as the standard and extended motion parameters estimated during preprocessing. The following contrasts were estimated: passive viewing, load 1, load 2, tracking ([load 1 + load 2] – passive viewing) and load (load 2 – load 1). To estimate main effects of experimental conditions across individuals contrasts of parameter estimates (COPEs) from each participant's first scan session (baseline) were submitted to a mixed effects analysis using FMRIB's Local Analysis of Mixed Effects, estimating group level parameters. To test for differences in brain activation before (scan session 2) and after (scan session 3) training, we first performed fixed effects analysis for each participant separately, including all COPEs from first level GLM, specifying the contrasts session 3 minus session 2. Next, all individual COPE maps were submitted to randomise to test for main effects while correcting for multiple comparisons using permutation testing and threshold free cluster enhancement (TFCE (Smith and Nichols, 2009)).

To quantify within-subject reliability in brain activation, we estimated intraclass correlation coefficient (ICC) for each voxel between assessment two and three utilizing the

variance from one-way random ANOVA, for the contrasts passive viewing, load 1 and load 2, as implemented in the ICCest function from the ICC R package (Wolak et al., 2012).

To test for associations between Cogmed change and average performance scores and brain activation, individual level COPE maps were stacked and submitted to randomise. The model included sex, age, and either Cogmed change score or Cogmed average performance score (obtained from the PCA). All models were corrected for multiple comparisons across space using 5000 permutations and thresholded using TFCE.

Results

Cogmed performance

Figure 3 shows Cogmed performance over time for each group and Table 2 displays corresponding summary statistics. Lme revealed a significant group-level improvement on all Cogmed tests included in the analysis. In addition, we found a significant association with age on mean performance across all tests, indicating lower average performance with higher age. We found no significant associations between Cogmed performance and sex, tDCS group (sham/experimental), or years of education. We found a significant interaction between time and tDCS on the twist task, suggesting augmented training gain in the participants in the active tDCS stimulation group. However, after removal of one outlier defined by visual inspection, the result did not reach significance (see Supplementary Table 1 and Supplementary Figure 4 for corresponding statistics and visualization).

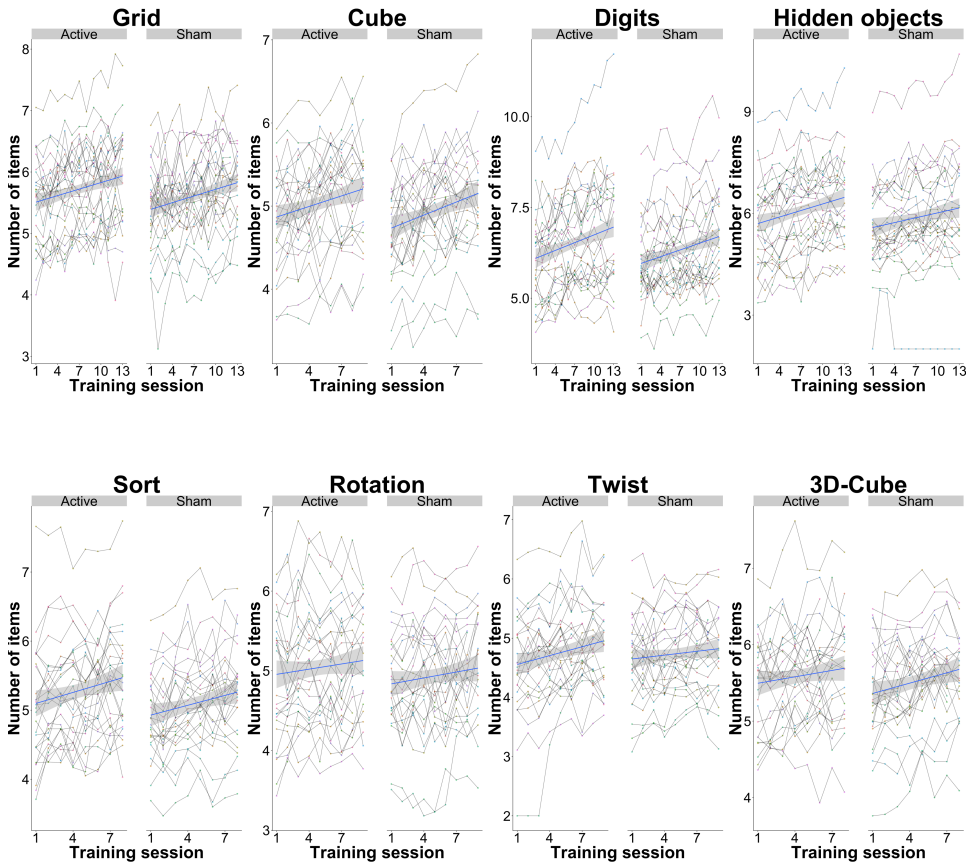

Figure 3. Individual level task performance during the course of the intervention period for each group (tDCS sham/active). The fit lines are based on a linear fit within each group.

	Grid	Sort	Digits	Cube	Hidden objects	Twist	3D-Cube	Rotation
Session	**8.66** ***(<0.001)***	**6.40** ***(<0.001)***	**12.79** ***(<0.001)***	**7.44** ***(<0.001)***	**11.03** ***(<0.001)***	**6.45** ***(<0.001)***	**3.16** ***(0.002)***	**2.21** ***(0.028)***
Age	**-3.05** ***(0.004)***	**-2.11** ***(0.041)***	**-6.07** ***(<0.001)***	**-2.54** ***(0.015)***	**-4.86** ***(<0.001)***	**-3.62** ***(0.001)***	**-3.90** ***(<0.001)***	**-3.41** ***(0.001)***
Sex	-0.89 (0.377)	-0.33 (0.741)	-2.29 (0.027)	-1.22 (0.23)	-2.25 (0.029)	-1.46 (0.15)	-1.42 (0.162)	-1.34 (0.187)
tDCS	-0.65 (0.521)	-1.03 (0.309)	-0.06 (0.951)	-0.53 (0.599)	0.12 (0.908)	1.00 (0.324)	-0.82 (0.414)	-0.81 (0.422)
Education	0.06 (0.951)	0.96 (0.34)	0.90 (0.374)	0.14 (0.886)	1.57 (0.124)	0.01 (0.991)	-0.15 (0.884)	0.33 (0.744)
Session x tDCS	0.2 (0.842)	-0.39 (0.7)	-1.53 (0.128)	0.46 (0.644)	-1.79 (0.074)	**-2.83** **(0.005)**	1.72 (0.087)	1.23 (0.22)

Table 2. Summary stats from linear mixed effects models testing for associations between task performance and session, age, sex, tDCS, education and the interaction between session and tDCS. Raw p-vaules are displayed, significant findings are highlighted (FDR-corrected, alpha = 0.05).

We found no significant correlation between Cogmed average performance and Cogmed change score (r=.17, t=1.29, p=.2). We found a significant association between lesion volume and Cogmed change score (t -2.5, p=.017), which did not retain significance after removal of one outlier (t=-.58, p=.563). See Supplementary Table 2 for corresponding statistics.

fMRI main effects of task

Figure 4 shows main effects of task condition at baseline, and Table 3 summarizes anatomical location. Passive viewing was associated with increased activity in the dorsal attention network (DAN) and the inferior and superior occipital cortex, and decreased activation in pre and post-central gyrus, supplementary motor area (SMA), anterior cingulate, as well as default mode network (DMN), including posterior cingulate gyrus (PCC), medial prefrontal gyrus (mPFC), and superior and medial temporal gyrus (S/MTG).

Load 1 was associated with increased activity in DAN, extending into the inferior and superior occipital cortex, cerebellum, and precentral gyrus, in the cingulo-opercular (CO) network, including thalamus, frontal operculum and insula, as well as in the ventral attention (VAN) network including temporoparietal junction and supramarginal gyrus, middle frontal gyrus, and frontal operculum. Decreased activity was seen in DMN nodes including PCC, mPFC and S/MTG. Load 2 showed a similar pattern to Load 1, with additional increased activation in right anterior middle frontal gyrus. Tracking over passive viewing revealed same activation pattern as load 1 and load 2, with additional bilateral activation of anterior middle frontal gyrus. Load-related (load 2 –load1) increases in activation were seen in superior and inferior parietal lobe, as well as right anterior middle frontal gyrus in response to increased cognitive demands, with no significant load-dependent decreases in activation.

Our analysis revealed no significant differences in brain activation between timepoint 2 and timepoint 3 for any of the task contrasts.

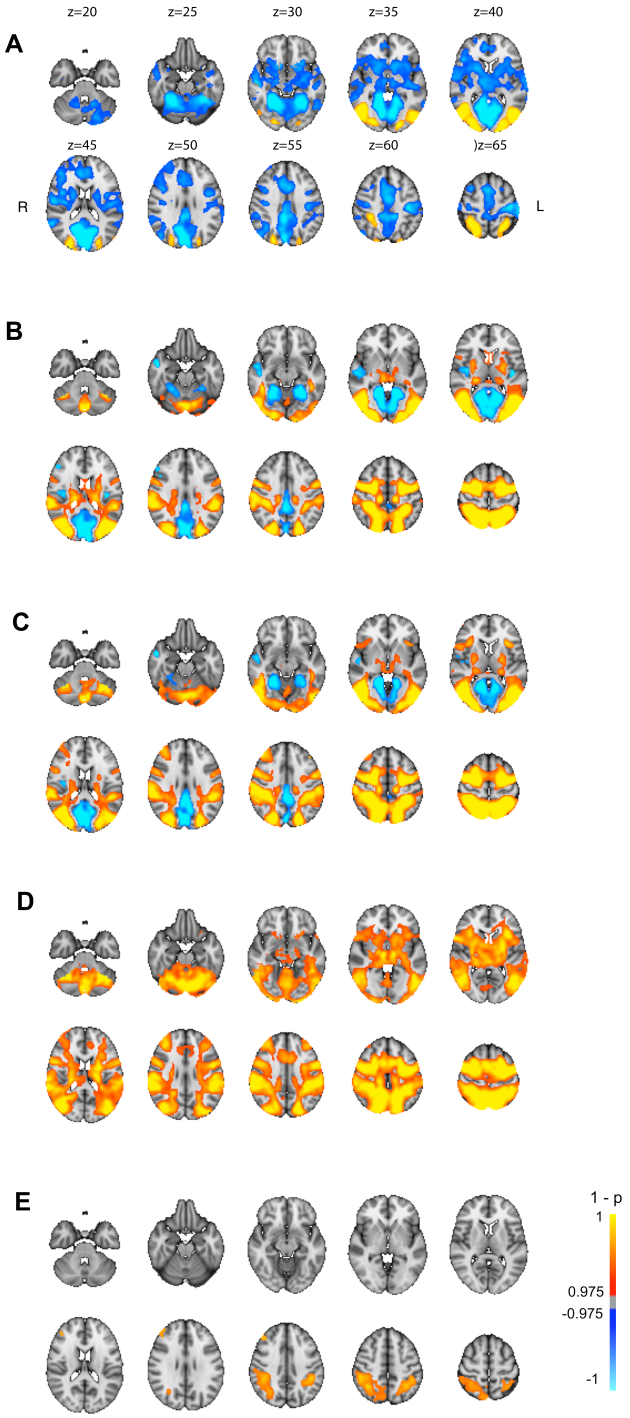

Figure 4. Main effects from task-fMRI for respectively passive viewing (A), load 1 (B), load 2 (C), tracking over passive viewing (D), and increase in task difficulty (E). Panel A display corresponding coordinates in MNI, and left / right orientation.

Condition	Direction	size	X	Y	Z	Area
PV	pos	4029	33	19	30	Lateral occipital cortex
	pos	3861	55	18	32	Lateral occipital cortex
	pos	1784	29	41	61	Superior parietal lobe
	neg	64337	33	35	21	Cerebellum
Load1	pos	57023	59	29	8	Cerebellum
	neg	12615	33	39	23	Cerebellum
	neg	1494	19	62	24	Middle temporal gyrus
	neg	256	65	53	42	Central opercular cortex
	neg	153	20	78	48	Middle frontal gyrus
	neg	19	22	71	50	Inferior frontal gyrus
Load2	pos	66242	59	29	8	Cerebellum
	pos	411	65	71	37	Frontal operculum
	pos	8	65	80	55	Middle frontal gyrus
	neg	10269	31	40	26	Occipital fusiform cortex
	neg	694	18	63	26	Superior temporal gyrus
Tracking	pos	101656	59	29	8	Cerebellum
Load	pos	4590	24	42	55	Inferior parietal lobe
	pos	1709	67	42	56	Inferior parietal lobe
	pos	245	24	79	54	Middle frontal gyrus

Table 3. Clusters associated with different MOT condition at baseline (all $p<.05$, corrected)

fMRI – reliability

Figure 5 shows voxel-wise ICC for COPE values for passive viewing, load 1 and load 2, between timepoint 2 and 3. The results revealed ICC>0.3 across major portions of the brain, including occipital, temporal, parietal and a large part of the frontal lobes.

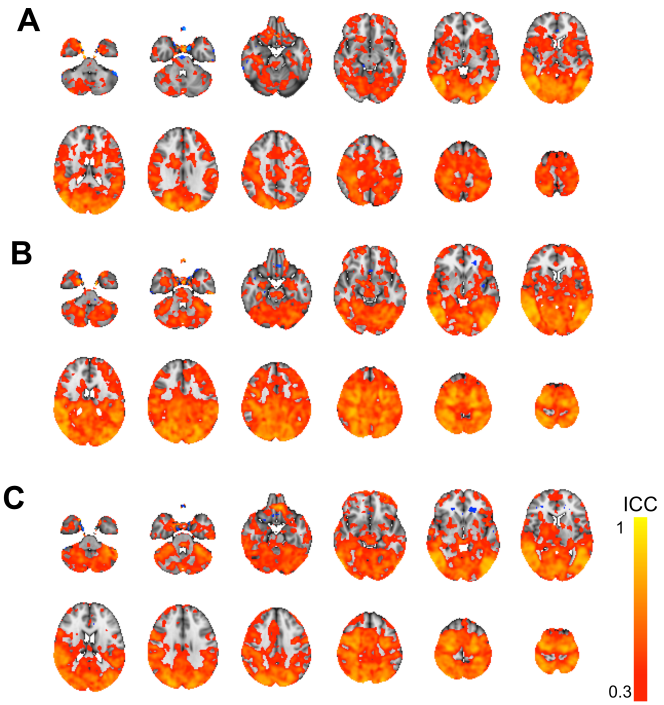

Figure 5. Voxel-wise ICC for condition passive viewing (A), load 1 (B), and load 2 (C). Only ICC values above 0.3 are displayed. Fig 4A displays corresponding coordinates in MNI, and left / right orientation.

Cogmed –fMRI associations

We found no significant associations between the Cogmed change score and brain activation at timepoint 1, or between Cogmed change score and the difference in brain activation between timepoint 2 and 3.

Likewise, we found no significant associations between Cogmed average performance score and brain activation at timepoint 1. However, the results revealed a significant association between Cogmed average performance score and the difference in activation during attentive tracking between timepoint 2 and 3, indicating larger activation increases in the anterior cingulate cortex (ACC) (Figure 6) with higher average performance. For transparency, the same analysis utilizing the Cogmed average performance score based on all 8 subtests (from the PCA), revealed highly similar effects (Supplementary Figure 5), suggesting that the results were not reliant or biased by excluding the two subtests.

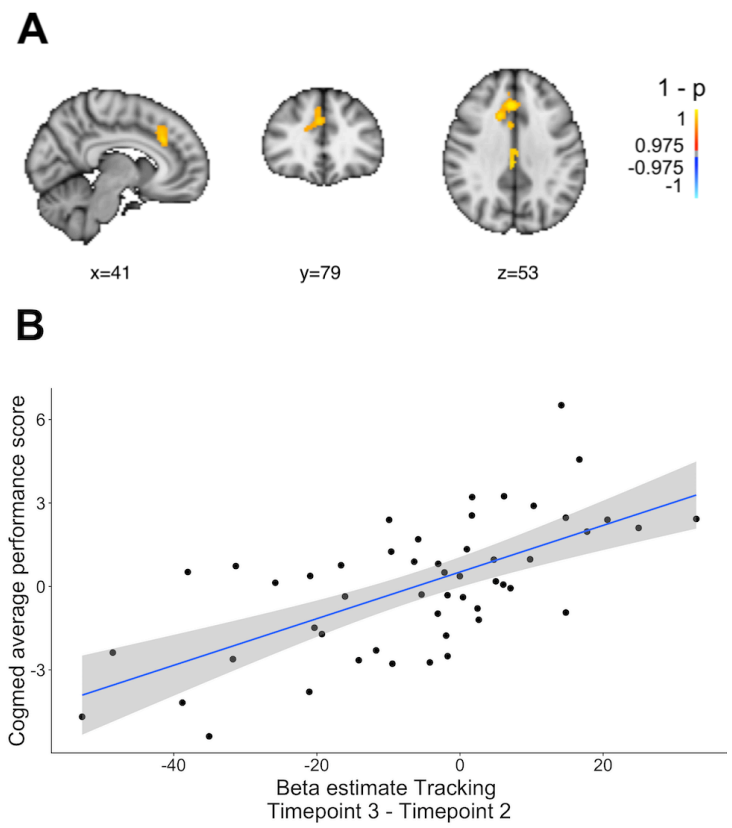

Figure 6. (A) Association between Cogmed average performance score, and difference in activation due to task engagement between timepoint 3 and 2, and (B) Scatterplot between Cogmed average performance score, and average beta-value in the significant cluster displayed in A.

Discussion

In this study, we tested the feasibility and effectiveness of a commercially available working memory-training package paired with tDCS in a heterogeneous group of chronic stroke survivors. Further, we assessed the predictive value of fMRI-based brain activation pre-training on training related gains, as well as changes in task activations between pre and post training. The results revealed significant performance gains on the trained tasks. Further, we found no additional gain of tDCS on training gain. Of note, albeit non-significant, the directionality of the effects indicated no clear direction of tDCS effects. Our analysis revealed no significant association between fMRI brain activation prior to training and performance gain, nor average performance during the training period. However, high average performance across the training sessions was associated with increased task activation from pre to post-training in the ACC.

Tailoring behavioral interventions for alleviating cognitive difficulties following stroke calls for investigation of both treatment response, as well as delineating factors predicting favorable outcome. Cognitive abilities prior to training as well as motivation (Guye et al., 2017; Jaeggi et al., 2014) are currently among our best predictors for beneficial effects. Our results revealed significant improvement on all included tasks from the training program, in line with previous reports (Spencer-Smith and Klingberg, 2015; Westerberg et al., 2007). Our results support that repeated practice, where level of difficulty is adjusted during training, improves performance on the trained tasks. However, the generalizability of training-effects following CCT has been debated (Au et al., 2015; Melby-Lervåg and Hulme, 2013; Morrison and Chein, 2011; Shipstead et al., 2012; von Bastian and Oberauer, 2014). Indeed, recent large-scale reviews suggest a lack of reliable transfer beyond tasks that share properties with the trained tasks (Melby-Lervåg et al., 2016; Sala and Gobet, 2018). The lack of transfer effects is suggested to be caused by the failure of targeting common mechanisms underlying fluid intelligence such as working memory and attention, and rather targeting task specific mechanisms through repeated practice (Melby-Lervåg et al., 2016). Despite our promising behavioral results on trained tasks, the previous lack of transfer-effects calls for caution before implementation in a clinical setting.

With the exception of one of the trained tasks, that did not reach significance after removal of an outlier, our results revealed no significant interaction between cognitive improvement and tDCS stimulation. Although anodal tDCS has shown beneficial effects on cognitive training compared with sham stimulation in healthy adults (Martin et al., 2013) and have been associated with steeper learning curves (Ruf et al., 2017), a recent meta-analysis provided no support of a beneficial effect of tDCS on cognitive training compared to sham (Medina and Cason, 2017). The current literature investigating the added effect of combining tDCS and working memory training in stroke patients is scarce. Single session anodal tDCS towards the left DLPFC improved recognition accuracy during an N-back task (Jo et al.,

2009), and longitudinal concurrent anodal tDCS and CCT increased accuracy on a non-trained continuous performance test (CPT) compared to sham (Park et al., 2013). However divergence in study protocols and results hampers a direct comparison (daSilva Filho et al., 2017). Beyond robust improvement on all trained tasks during the course of the intervention, our results provide no evidence of additional beneficial effects of tDCS stimulation.

Our fMRI results revealed increased activation of the DAN, along with deactivation of DMN for passive viewing, load 1 and load 2. Further, contrasting tracking to passive viewing, and load 2 to load 1 revealed that attentive tracking increased DAN activation in a load-dependent manner, in line with previous reports based on healthy samples (Alnæs et al., 2014; Dørum et al., 2016). Higher average Cogmed task performance was associated with increased tracking-related ACC activation following training. Working memory performance has been associated with increased activity in ACC, in particular for error monitoring and task set maintenance (D'Esposito et al., 1995; Kolling et al., 2016).

Studies delineating developmental trajectories of working memory indicate that healthy development entails an age-related increase in working memory related activity and connectivity in ACC, and is associated with increases in cognitive capacity (Kolskår et al., 2018). ACC activation has also been linked to intelligence in healthy adults (Basten et al., 2015), and stronger ACC recruitment was associated with increased attention following CCT in patients with ADHD (Stevens et al., 2016). Similarly, longitudinal fMRI during a working memory task revealed increased ACC activation in parallel with training gains in adults with ADHD (Zilverstand et al., 2017). Taken together, these and our findings indicate that WM capacity is associated with neural modulation of ACC in response to WM task performance.

The current findings should be interpreted in light of several limitations. Based on the clinical ratings (NIHSS) at hospital discharge, the patient group was sampled from the less severe part of the stroke severity spectrum. Further, patient drop-out during the intervention was due to the labor-intensity of the training. Hence, our sample is biased towards higher

functioning stroke patients, limiting the generalizability of our results. The lack of a control group for the CCT does not allow us to disentangle effects of the cognitive training from the effect of time, anticipation, or other confounders. Further, the current study does not investigate transfer effects of the cognitive training that may be relevant for evaluating clinical relevance, and further studies are needed to evaluate the full behavioral potential for working memory interventions in stroke patients. The group level task activation patterns in the current study largely mirrored those reported in previous studies in healthy controls (Alnæs et al., 2015a; Dørum et al., 2016). However, the current study design did not allow us to make an explicit comparison (D'Esposito et al., 2003). Here we only considered brain activation in response to task demands. Future studies should also pursue a promising line of research utilizing imaging indices of structural and functional connectivity to investigate behavioral correlates of stroke, which may supplement and increase our understanding of stroke and stroke recovery.

In conclusion, we have investigated response to a computerized cognitive training program in 54 stroke survivors in combination with tDCS, as well as the predictive value of neural activation on training outcome, and neural alterations following training. Our results revealed increased performance across all trained tasks. However, the generalizability of CCT has previously been questioned, which, combined with the lack of tDCS effects in the current study, calls for caution when interpreting the clinical relevance. We found no significant predictive value of brain activation prior to training on training outcome, but average performance across trained tasks was related to increased ACC activation following training.

References

Adams, H.P., Bendixen, B.H., Kappelle, L.J., Biller, J., Love, B.B., Gordon, D.L., Marsh, E.E., 1993. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 24, 35-41.

Alnæs, D., Kaufmann, T., Richard, G., Duff, E.P., Sneve, M.H., Endestad, T., Nordvik, J.E., Andreassen, O.A., Smith, S.M., Westlye, L.T., 2015a. Attentional load modulates large-scale functional brain connectivity beyond the core attention networks. NeuroImage 109, 260-272.
Alnæs, D., Sneve, M.H., Espeseth, T., Endestad, T., van de Pavert, S.H.P., Laeng, B., 2014. Pupil size signals mental effort deployed during multiple object tracking and predicts brain activity in the dorsal attention network and the locus coeruleus. Journal of Vision 14, 1-1.
Alnæs, D., Sneve, M.H., Richard, G., Skåtun, K.C., Kaufmann, T., Nordvik, J.E., Andreassen, O.A., Endestad, T., Laeng, B., Westlye, L.T., 2015b. Functional connectivity indicates differential roles for the intraparietal sulcus and the superior parietal lobule in multiple object tracking. NeuroImage 123, 129-137.
Altamura, C., Reinhard, M., Vry, M.-S., Kaller, C.P., Hamzei, F., Vernieri, F., Rossini, P.M., Hetzel, A., Weiller, C., Saur, D., 2009. The longitudinal changes of BOLD response and cerebral hemodynamics from acute to subacute stroke. A fMRI and TCD study. BMC Neuroscience 10, 151.
Andrews, S.C., Hoy, K.E., Enticott, P.G., Daskalakis, Z.J., Fitzgerald, P.B., 2011. Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. Brain Stimulation 4, 84-89.
Au, J., Sheehan, E., Tsai, N., Duncan, G.J., Buschkuehl, M., Jaeggi, S.M., 2015. Improving fluid intelligence with training on working memory: a meta-analysis. Psychonomic Bulletin & Review 22, 366-377.
Barbay, M., Diouf, M., Roussel, M., Godefroy, O., 2018. Systematic Review and Meta-Analysis of Prevalence in Post-Stroke Neurocognitive Disorders in Hospital-Based Studies. Dementia and Geriatric Cognitive Disorders 46, 322-334.
Basten, U., Hilger, K., Fiebach, C.J., 2015. Where smart brains are different: A quantitative meta-analysis of functional and structural brain imaging studies on intelligence. Intelligence 51, 10-27.
Buitenweg, J.I.V., Van De Ven, R.M., Ridderinkhof, K.R., Murre, J.M.J., 2018. Does cognitive flexibility training enhance subjective mental functioning in healthy older adults? Aging, Neuropsychology, and Cognition, 1-23.
Clas, P., Groeschel S Fau - Wilke, M., Wilke, M., 2012. A semi-automatic algorithm for determining the demyelination load in metachromatic leukodystrophy. Academic Radiology 19.
Constantinidis, C., Klingberg, T., 2016. The neuroscience of working memory capacity and training. Nature Reviews Neuroscience 17, 438.
D'Esposito, M., Deouell, L.Y., Gazzaley, A., 2003. Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. Nature Reviews Neuroscience 4, 863.
D'Esposito, M., Detre, J.A., Alsop, D.C., Shin, R.K., Atlas, S., Grossman, M., 1995. The neural basis of the central executive system of working memory. Nature 378, 279.
daSilva Filho, E.M., Andrade deAlbuquerque, J., Mescouto, K.A., deAbreu Freitas, R.P., 2017. Effects of transcranial direct current stimulation on the working memory of post-stroke people: an integrative review. Manual Therapy, Posturology & Rehabilitation Journal= Revista Manual Therapy 15.
de Haan, B., Clas, P., Juenger, H., Wilke, M., Karnath, H.-O., 2015. Fast semi-automated lesion demarcation in stroke. NeuroImage. Clinical 9, 69-74.
De Luca, R., Calabrò, R.S., Bramanti, P., 2018a. Cognitive rehabilitation after severe acquired brain injury: current evidence and future directions. Neuropsychological Rehabilitation 28, 879-898.
De Luca, R., Leonardi, S., Spadaro, L., Russo, M., Aragona, B., Torrisi, M., Maggio, M.G., Bramanti, A., Naro, A., De Cola, M.C., Calabrò, R.S., 2018b. Improving Cognitive Function in Patients with Stroke: Can Computerized Training Be the Future? Journal of Stroke and Cerebrovascular Diseases 27, 1055-1060.

Dedoncker, J., Brunoni, A.R., Baeken, C., Vanderhasselt, M.-A., 2016. A Systematic Review and Meta-Analysis of the Effects of Transcranial Direct Current Stimulation (tDCS) Over the Dorsolateral Prefrontal Cortex in Healthy and Neuropsychiatric Samples: Influence of Stimulation Parameters. Brain Stimulation 9, 501-517.
Dørum, E.S., Alnæs, D., Kaufmann, T., Richard, G., Lund, M.J., Tønnesen, S., Sneve, M.H., Mathiesen, N.C., Rustan, Ø.G., Gjertsen, Ø., Vatn, S., Fure, B., Andreassen, O.A., Nordvik, J.E., Westlye, L.T., 2016. Age-related differences in brain network activation and co-activation during multiple object tracking. Brain and Behavior 6, e00533.
Feigin, V.L., Norrving, B., Mensah, G.A., 2017. Global Burden of Stroke. Circulation Research 120, 439.
Fregni, F., Boggio Ps Fau - Nitsche, M., Nitsche M Fau - Bermpohl, F., Bermpohl F Fau - Antal, A., Antal A Fau - Feredoes, E., Feredoes E Fau - Marcolin, M.A., Marcolin Ma Fau - Rigonatti, S.P., Rigonatti Sp Fau - Silva, M.T.A., Silva Mt Fau - Paulus, W., Paulus W Fau - Pascual-Leone, A., Pascual-Leone, A., 2005. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Experimental Brain Research.
Giordano, J., Bikson, M., Kappenman, E.S., Clark, V.P., Coslett, H.B., Hamblin, M.R., Hamilton, R., Jankord, R., Kozumbo, W.J., McKinley, R.A., Nitsche, M.A., Reilly, J.P., Richardson, J., Wurzman, R., Calabrese, E., 2017. Mechanisms and Effects of Transcranial Direct Current Stimulation. Dose-Response 15, 1559325816685467.
Goldstein, L.B., Bertels, C., Davis, J.N., 1989. Interrater Reliability of the NIH Stroke Scale. Archives of Neurology 46, 660-662.
Guye, S., De Simoni, C., von Bastian, C.C., 2017. Do Individual Differences Predict Change in Cognitive Training Performance? A Latent Growth Curve Modeling Approach. Journal of Cognitive Enhancement 1, 374-393.
Haut, K.M., Lim, K.O., MacDonald Iii, A., 2010. Prefrontal Cortical Changes Following Cognitive Training in Patients with Chronic Schizophrenia: Effects of Practice, Generalization, and Specificity. Neuropsychopharmacology 35, 1850.
Heinzel, S., Lorenz, R.C., Pelz, P., Heinz, A., Walter, H., Kathmann, N., Rapp, M.A., Stelzel, C., 2016. Neural correlates of training and transfer effects in working memory in older adults. NeuroImage 134, 236-249.
Hill, A.T., Fitzgerald, P.B., Hoy, K.E., 2016. Effects of Anodal Transcranial Direct Current Stimulation on Working Memory: A Systematic Review and Meta-Analysis of Findings From Healthy and Neuropsychiatric Populations. Brain Stimulation 9, 197-208.
Jaeggi, S.M., Buschkuehl, M., Shah, P., Jonides, J., 2014. The role of individual differences in cognitive training and transfer. Memory & Cognition 42, 464-480.
Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. NeuroImage 17, 825-841.
Jenkinson, M., Beckmann, C.F., Behrens, T.E.J., Woolrich, M.W., Smith, S.M., 2012. FSL. NeuroImage 62, 782-790.
Jenkinson, M., Smith, S., 2001. A global optimisation method for robust affine registration of brain images. Medical Image Analysis 5, 143-156.
Jo, J.M., Kim, Y.-H., Ko, M.-H., Ohn, S.H., Joen, B., Lee, K.H., 2009. Enhancing the Working Memory of Stroke Patients Using tDCS. American Journal of Physical Medicine & Rehabilitation 88.
Kang, N., Summers, J.J., Cauraugh, J.H., 2015. Transcranial direct current stimulation facilitates motor learning post-stroke: a systematic review and meta-analysis. Journal of Neurology, Neurosurgery & Psychiatry.
Kolling, N., Wittmann, M.K., Behrens, T.E.J., Boorman, E.D., Mars, R.B., Rushworth, M.F.S., 2016. Value, search, persistence and model updating in anterior cingulate cortex. Nature Neuroscience 19, 1280.

Kolskår, K.K., Alnæs, D., Kaufmann, T., Richard, G., Sanders, A.-M., Ulrichsen, K.M., Moberget, T., Andreassen, O.A., Nordvik, J.E., Westlye, L.T., 2018. Key Brain Network Nodes Show Differential Cognitive Relevance and Developmental Trajectories during Childhood and Adolescence. eNeuro.
Lawrence, B.J., Gasson, N., Johnson, A.R., Booth, L., Loftus, A.M., 2018. Cognitive Training and Transcranial Direct Current Stimulation for Mild Cognitive Impairment in Parkinson's Disease: A Randomized Controlled Trial. Parkinson's Disease 2018.
Leung, I.H.K., Walton, C.C., Hallock, H., Lewis, S.J.G., Valenzuela, M., Lampit, A., 2015. Cognitive training in Parkinson disease: A systematic review and meta-analysis. Neurology 85, 1843-1851.
Lin, Z.C., Tao, J., Gao, Y.L., Yin, D.Z., Chen, A.Z., Chen, L.D., 2014. Analysis of central mechanism of cognitive training on cognitive impairment after stroke: Resting-state functional magnetic resonance imaging study. Journal of International Medical Research 42.
Maffei, L., Picano, E., Andreassi, M.G., Angelucci, A., Baldacci, F., Baroncelli, L., Begenisic, T., Bellinvia, P.F., Berardi, N., Biagi, L., Bonaccorsi, J., Bonanni, E., Bonuccelli, U., Borghini, A., Braschi, C., Broccardi, M., Bruno, R.M., Caleo, M., Carlesi, C., Carnicelli, L., Cartoni, G., Cecchetti, L., Cenni, M.C., Ceravolo, R., Chico, L., Cintoli, S., Cioni, G., Coscia, M., Costa, M., D'Angelo, G., D'Ascanio, P., Nes, M.D., Turco, S.D., Coscio, E.D., Galante, M.D., Lascio, N.d., Faita, F., Falorni, I., Faraguna, U., Fenu, A., Fortunato, L., Franco, R., Gargani, L., Gargiulo, R., Ghiadoni, L., Giorgi, F.S., Iannarella, R., Iofrida, C., Kusmic, C., Limongi, F., Maestri, M., Maffei, M., Maggi, S., Mainardi, M., Mammana, L., Marabotti, A., Mariotti, V., Melissari, E., Mercuri, A., Micera, S., Molinaro, S., Narducci, R., Navarra, T., Noale, M., Pagni, C., Palumbo, S., Pasquariello, R., Pellegrini, S., Pietrini, P., Pizzorusso, T., Poli, A., Pratali, L., Retico, A., Ricciardi, E., Rota, G., Sale, A., Sbrana, S., Scabia, G., Scali, M., Scelfo, D., Sicari, R., Siciliano, G., Stea, F., Taddei, S., Tognoni, G., Tonacci, A., Tosetti, M., Turchi, S., Volpi, L., 2017. Randomized trial on the effects of a combined physical/cognitive training in aged MCI subjects: the Train the Brain study. Scientific Reports 7, 39471.
Mahon, S., Parmar, P., Barker-Collo, S., Krishnamurthi, R., Jones, K., Theadom, A., Feigin, V., 2017. Determinants, Prevalence, and Trajectory of Long-Term Post-Stroke Cognitive Impairment: Results from a 4-Year Follow-Up of the ARCOS-IV Study. Neuroepidemiology 49, 129-134.
Marquez, J., van Vliet, P., McElduff, P., Lagopoulos, J., Parsons, M., 2015. Transcranial Direct Current Stimulation (tDCS): Does it Have Merit in Stroke Rehabilitation? A Systematic Review. International Journal of Stroke 10, 306-316.
Martin, D.M., Liu, R., Alonzo, A., Green, M., Player, M.J., Sachdev, P., Loo, C.K., 2013. Can transcranial direct current stimulation enhance outcomes from cognitive training? A randomized controlled trial in healthy participants. International Journal of Neuropsychopharmacology 16, 1927-1936.
Medina, J., Cason, S., 2017. No evidential value in samples of transcranial direct current stimulation (tDCS) studies of cognition and working memory in healthy populations. Cortex 94, 131-141.
Melby-Lervåg, M., Hulme, C., 2013. Is working memory training effective? A meta-analytic review. Developmental Psychology 49, 270-291.
Melby-Lervåg, M., Redick, T.S., Hulme, C., 2016. Working Memory Training Does Not Improve Performance on Measures of Intelligence or Other Measures of "Far Transfer": Evidence From a Meta-Analytic Review. Perspectives on Psychological Science 11, 512-534.
Miró-Padilla, A., Bueichekú, E., Ventura-Campos, N., Flores-Compañ, M.-J., Parcet, M.A., Ávila, C., 2018. Long-term brain effects of N-back training: an fMRI study. Brain Imaging and Behavior.

Morrison, A.B., Chein, J.M., 2011. Does working memory training work? The promise and challenges of enhancing cognition by training working memory. Psychonomic Bulletin & Review 18, 46-60.
Motes, M.A., Yezhuvath, U.S., Aslan, S., Spence, J.S., Rypma, B., Chapman, S.B., 2018. Higher-order cognitive training effects on processing speed–related neural activity: a randomized trial. Neurobiology of Aging 62, 72-81.
Motter, J.N., Pimontel, M.A., Rindskopf, D., Devanand, D.P., Doraiswamy, P.M., Sneed, J.R., 2016. Computerized cognitive training and functional recovery in major depressive disorder: A meta-analysis. Journal of Affective Disorders 189, 184-191.
Ørbeck, B., Sundet, K., 2007. WASI (Wechsler Abbreviated Scale of Intelligence) Norsk versjon Manualsupplement. Stockholm: Harcort Asessment Inc.
P. Filzmoser, Gschwandtner, M., 2018. mvoutlier: Multivariate Outlier Detection Based on Robust Methods.
Park, S.H., Koh, E.J., Choi, H.Y., Ko, M.H., 2013. A double-blind, sham-controlled, pilot study to assess the effects of the concomitant use of transcranial direct current stimulation with the computer assisted cognitive rehabilitation to the prefrontal cortex on cognitive functions in patients with stroke. J Korean Neurosurg Soc. 54.
Peers, P.V., Astle, D.E., Duncan, J., Murphy, F., Hampshire, A., Das, T., Manly, T., 2018. A randomised exploratory investigation of the effects of Attention vs Working Memory Training on cognitive performance and everyday functioning following stroke. bioRxiv.
Pendlebury, S.T., 2012. Dementia in Patients Hospitalized with Stroke: Rates, Time Course, and Clinico-Pathologic Factors. International Journal of Stroke 7, 570-581.
Pinheiro, J., Bates, D., DebRoy, S., Sarkar, D., Team, R.C., 2017. nlme: Linear and Nonlinear Mixed Effects Models - R package version 3.1-131.
Prikken, M., Konings, M.J., Lei, W.U., Begemann, M.J.H., Sommer, I.E.C., 2018. The efficacy of computerized cognitive drill and practice training for patients with a schizophrenia-spectrum disorder: A meta-analysis. Schizophrenia Research.
Pylyshyn, Z.W., Storm, R.W., 1988. Tracking multiple independent targets: evidence for a parallel tracking mechanism.
Ramsay, I.S., MacDonald, I.I.I.A.W., 2015. Brain Correlates of Cognitive Remediation in Schizophrenia: Activation Likelihood Analysis Shows Preliminary Evidence of Neural Target Engagement. Schizophrenia Bulletin 41, 1276-1284.
Ruf, S.P., Fallgatter, A.J., Plewnia, C., 2017. Augmentation of working memory training by transcranial direct current stimulation (tDCS). Scientific Reports 7, 876.
Sala, G., Gobet, F., 2018. Cognitive Training Does Not Enhance General Cognition. Trends in Cognitive Sciences.
Schaapsmeerders, P., Maaijwee Na Fau - van Dijk, E.J., van Dijk Ej Fau - Rutten-Jacobs, L.C.A., Rutten-Jacobs Lc Fau - Arntz, R.M., Arntz Rm Fau - Schoonderwaldt, H.C., Schoonderwaldt Hc Fau - Dorresteijn, L.D.A., Dorresteijn Ld Fau - Kessels, R.P.C., Kessels Rp Fau - de Leeuw, F.-E., de Leeuw, F.E., 2013. Long-term cognitive impairment after first-ever ischemic stroke in young adults. Stroke 44.
Shipstead, Z., Hicks, K.L., Engle, R.W., 2012. Cogmed working memory training: Does the evidence support the claims? Journal of Applied Research in Memory and Cognition 1, 185-193.
Smith, S.M., Brady, J.M., 1997. SUSAN—A New Approach to Low Level Image Processing. International Journal of Computer Vision 23, 45-78.
Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 23, Supplement 1, S208-S219.

Smith, S.M., Nichols, T.E., 2009. Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. NeuroImage 44, 83-98.
Spencer-Smith, M., Klingberg, T., 2015. Benefits of a Working Memory Training Program for Inattention in Daily Life: A Systematic Review and Meta-Analysis. PLOS ONE 10, e0119522.
Stevens, M.C., Gaynor, A., Bessette, K.L., Pearlson, G.D., 2016. A preliminary study of the effects of working memory training on brain function. Brain Imaging and Behavior 10, 387-407.
Strobel, K., Engedal, K., 2008. MMSE-NR, Norsk revidert Mini Mental Status Evaluering. Book MMSE-NR, Norsk revidert Mini Mental Status Evaluering. Oslo: Nasjonal kompetansetjeneste i aldring og helse.
Subramaniam, K., Luks, T.L., Garrett, C., Chung, C., Fisher, M., Nagarajan, S., Vinogradov, S., 2014. Intensive cognitive training in schizophrenia enhances working memory and associated prefrontal cortical efficiency in a manner that drives long-term functional gains. NeuroImage 99, 281-292.
Synhaeve, N.E., Arntz Rm Fau - Maaijwee, N.A.M., Maaijwee Na Fau - Rutten-Jacobs, L.C.A., Rutten-Jacobs Lc Fau - Schoonderwaldt, H.C., Schoonderwaldt Hc Fau - Dorresteijn, L.D.A., Dorresteijn Ld Fau - de Kort, P.L.M., de Kort Pl Fau - van Dijk, E.J., van Dijk Ej Fau - de Leeuw, F.-E., de Leeuw, F.E., 2014. Poor long-term functional outcome after stroke among adults aged 18 to 50 years: Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluation (FUTURE) study. Stroke 45.
Team, R.C., 2013. R: A language and environment for statistical computing
Teasell, R.W., 1992. Long-Term Sequelae of Stroke: How should you handle stroke complications? Canadian Family Physician 38, 381-388.
Ulrichsen, K.M., Alnæs, D., Kolskår, K.K., Richard, G., Sanders, A.M., Dørum, E.S., Ihle-Hansen, H., Pedersen, M.L., Tornås, S., Nordvik, J.E., Westlye, L.T., 2019. Dissecting the cognitive phenotype of post-stroke fatigue using drift diffusion modeling of sustained attention. bioRxiv 582502.
von Bastian, C.C., Oberauer, K., 2014. Effects and mechanisms of working memory training: a review. Psychological Research 78, 803-820.
Weicker, J., Villringer, A., Thöne-Otto, A., 2016. Can impaired working memory functioning be improved by training? A meta-analysis with a special focus on brain injured patients. Neuropsychology 30, 190-212.
Westerberg, H., Jacobaeus, H., Hirvikoski, T., Clevberger, P., Östensson, M.L., Bartfai, A., Klingberg, T., 2007. Computerized working memory training after stroke–A pilot study. Brain Injury 21, 21-29.
Wolak, M.E., Fairbairn, D.J., Paulsen, Y.R., 2012. Guidelines for Estimating Repeatability. Methods in Ecology and Evolution 3.
Woolrich, M.W., Ripley, B.D., Brady, M., Smith, S.M., 2001. Temporal Autocorrelation in Univariate Linear Modeling of FMRI Data. NeuroImage 14, 1370-1386.
Yang, S., Jiang, C., Ye, H., Tao, J., Huang, J., Gao, Y., Lin, Z., Chen, L., 2014. Effect of integrated cognitive therapy on hippocampal functional connectivity patterns in stroke patients with cognitive dysfunction: a resting-state FMRI study. Evidence-based complementary and alternative medicine : eCAM 2014, 962304-962304.
Ziemus, B., Baumann, O., Luerding, R., Schlosser, R., Schuierer, G., Bogdahn, U., Greenlee, M.W., 2007. Impaired working-memory after cerebellar infarcts paralleled by changes in BOLD signal of a cortico-cerebellar circuit. Neuropsychologia 45, 2016-2024.
Zilverstand, A., Sorger, B., Slaats-Willemse, D., Kan, C.C., Goebel, R., Buitelaar, J.K., 2017. fMRI Neurofeedback Training for Increasing Anterior Cingulate Cortex Activation in Adult

Attention Deficit Hyperactivity Disorder. An Exploratory Randomized, Single-Blinded Study. PLOS ONE 12, e0170795.
Zinn, S., Bosworth, H.B., Hoenig, H.M., Swartzwelder, H.S., 2007. Executive Function Deficits in Acute Stroke. Archives of Physical Medicine and Rehabilitation 88, 173-180.