A Longitudinal Study of Computerized Cognitive Training in Stroke Patients – Effects on Cognitive Function and White Matter

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Abstract

BACKGROUND: Computerized Cognitive Training is suggested to enhance attention and working memory functioning following stroke, but effects on brain and behavior are not sufficiently studied and longitudinal studies assessing brain and behavior relationships are scarce.

OBJECTIVE: The study objectives were to investigate relations between neuropsychological performance post stroke and white matter microstructure measures derived from diffusion tensor imaging (DTI), including changes after 6 weeks of working memory training.

METHODS: In this experimental training study, 26 stroke patients underwent DTI and neuropsychological tests at three time points – before and after a passive phase of 6 weeks, and again after 6 weeks of working memory training (Cogmed QM). Fractional Anisotropy (FA) was extracted from stroke-free brain areas to assess the white matter microstructure. 22 participants completed the majority of training (≥18/25 sessions) and were entered into longitudinal analyses.

RESULTS: Significant correlations between FA and baseline cognitive functions were observed ($r = 0.58$, $p = 0.004$), however no evidence was found of generally improved cognitive functions following training or of changes in white matter microstructure.

CONCLUSIONS: While white matter microstructure related to baseline cognitive function in stroke patients, the study revealed no effect on cognitive functions or microstructural changes in white matter in relation to computerized working memory training.

Keywords:

Stroke, Cognitive impairment, Diffusion tensor imaging, Cognitive rehabilitation, Working memory, Computerized cognitive training, Brain plasticity

Introduction

Literature from the last two decades points to stroke as an important cause of cognitive decline and dementia[1,2]. Cognitive impairments following stroke may prohibit survivors from being independent in activities of daily living and is associated with poor long-term outcome with higher disability and greater institutionalization rates[3,4]. While stroke remains a prominent cause of morbidity, the age-standardized rates of mortality seem to decrease worldwide, while the number of strokes each year still increases[4]. As the number of survivors with functional and cognitive impairments must be rising, so is the interest in finding good cognitive outcome predictors and rehabilitation options.

Several rehabilitation interventions to alleviate cognitive impairment have been studied[5-7], including Computerized Cognitive Training (CCT)[8], with diverging results, and little is known about the possible mechanisms behind potential improvement. CCT has in recent years been argued to be a good alternative or supplement to traditional cognitive rehabilitation, though studies have been conflicting to whether it boosts the capacity of cognitive functions or not[9,10]. Cogmed QM (Cogmed Systems AB, Stockholm, Sweden) is currently one of the most commonly used computerized working memory training systems, and preliminary evidence has shown that it can both improve objective working memory and attention[8]. Studies report significant effects of Cogmed QM on working memory in patients with acquired brain injury, including stroke[11-13].

The level of cognitive impairment following stroke likely depends on a multitude of factors, with site and size of lesion being insufficient to explain the outcome alone[14,15]. Microstructural characteristics of white matter tracts may contribute significantly to explain residual function[15-17], and further investigations of relations between such white matter characteristics and higher order cognitive function are needed.

Diffusion tensor imaging (DTI) is a MRI technique to quantitatively delineate the anatomy of white matter microstructure by measuring degree and directionality of diffusion. DTI fractional anisotropy (FA) has repeatedly been demonstrated to correlate with cognitive performance in patient groups, as well as in normal aging[18-20]. Relations between white matter integrity and cognitive performance following stroke have been presented in several studies[15,17,21]. Biological indicators like FA may play a key role in research on cognitive training, as they may serve as a satisfactory brain measure of training effect[19,22,23]. However, studies determining patterns of change in FA correlating with cognitive training post-stroke have been scarce. Two studies have studied brain changes in relation to CCT, and found that cognitive improvement after CCT was related to changes in white matter microstructure in a single case[24] and to functional changes in resting state in a group of stroke patients[25].

The research questions of the present study were: 1) Can relations between cognitive function and integrity in remaining white matter as measured by DTI be observed 1-6 years after stroke? 2) Will 6 weeks of training with the CCT program Cogmed QM, initiate objective cognitive improvement? 3) If so, does the observed cognitive change correspond with changes in white matter microstructure (FA)?

Materials and Methods

Sample

Initially 28 stroke patients were included in the study. Two participants opted out before baseline MRI because of lack of time. Twenty-six stroke patients (male=19, right handed=25, age range=18-65), previously admitted to Sunnaas Rehabilitation Hospitals and members of The Norwegian Association of Stroke Survivors (Landsforeningen for Slagrammede), were

included in baseline analyses and underwent DTI and neuropsychological tests at three time points – before and after a passive phase of 6 weeks, and again after 6 weeks of working memory training (Cogmed QM). Twenty-two finalized at least 70% of the training sessions (male=15, right handed=21), and were included in further analysis of training effects. See Table 1 for sample descriptive. Including those not completing 70% or more of the training in dropout statistics, a one-way ANOVA revealed that dropouts had a trend towards lower IQ-score ($p=0.081$) and bigger lesion size ($p=0.076$), but comparable age, global cognitive and working memory (WM) score and years of education.

The project was approved by the Regional Committee for Medical and Health Research Ethics, and the manuscript conforms to the STROBE Guidelines. Written informed consent was obtained from all participants. To reduce interference from spontaneous cognitive recovery[26-28], a minimum of 1 year since the stroke was required prior to the first assessment. Participants had to have full mobility in their dominant hand, be fluent Norwegian speakers, and have normal or corrected to normal vision, language and hearing. Other exclusion criteria were history of injury or disease known to affect CNS function, including previous strokes, dementia, neurological or psychiatric illness or serious head trauma. Participants were not to be under psychiatric treatment, use psychoactive drugs known to affect CNS functioning, or have any MRI contraindications.

Participants were included irrespective of type of stroke, with 76 % of patients having infarctions (n= 20), while 11.5 % (n=3) had suffered from intracerebral hemorrhage and subarachnoid hemorrhage (SAH) respectively.

Cognitive Training Software

Cogmed QM is an online working memory training program. The training consists of 25

sessions, typically to be completed in five weeks. The active time spent per session is approximately 40 min. Once a week there is an individual follow up appointment with a coach.

There are 12 different exercises. Four exercises were used for calculation of improvement in trained tasks, as they were present in all training sessions: "Grid" (visuospatial working memory); "Numbers" (verbal and visuospatial working memory); "Cube" (visuospatial working memory) and "Hidden numbers" (verbal working memory). The metrics of improvement in trained tasks were done for those completing 90% of the training days (minimum 22/25 days, n=20).

Neuropsychological Assessment

For assessment of general cognitive ability, Vocabulary subtest of the Wechsler Abbreviated Scale of intelligence (WASI) and Matrix reasoning subtest from Wechsler Adult Intelligence Scale – Third Edition (WASI-III) were used. The neuropsychological tests were mainly focused on working memory: Letter memory[29], a test adapted by Miyake et al.[30] from Morris and Jones[31]. Digit span with forwards and backwards condition (as measured by the Wechsler Memory Scale –Third Edition, WMS-III, Digit Span test)[32]; California Verbal Learning test (CVLT-II), analyses were done for the learning condition, and the 30 minutes free recall condition[33]; Rey Complex Figure Test (RCFT) recall score (visuospatial abilities and working memory)[34]; an n-back paradigm[35-37], using the 2-back and 3-back condition, with measures of accuracy and reaction time; the Spatial working memory test (SWM) from the Cambridge Neuropsychological Test Automated Battery (CANTAB[38]) were used as described elsewhere[39]. In addition were tests of executive functions included: The Plus-minus task (shifting)[40], adapted by Miyake et al.[30] from[41] and[42], the measure of each of the three

conditions: plus, minus and plus/minus were a measure of time controlled for number of mistakes; Stroop 4 and 3 (inhibition and shifting) corrected for speed by controlling for Stroop 1 and 2.

MRI Processing and Analysis

MRI-data were acquired as described in Appendix. The diffusion data were manually checked for major artifacts. Preprocessing of the typical noise artifacts, susceptibility distortions, eddy currents, and subject movement was performed with the FMRIB Software Library (FSL)[43-45].

Analysis of DTI data was performed using the FSL software package Tract-Based Spatial Statistics (TBSS)[46]. To allow for voxelwise comparisons across the white matter, all FA volumes were transformed into standard MNI152 space using nonlinear registration. Since this method requires stroke areas to be excluded, a semi-automatic algorithm was applied to obtain stroke masks from a combination of MP-RAGE and FLAIR scans. For detailed description on stroke masks see Appendix. The resulting stroke masks were also transformed into standard MNI152 space and added together to create a global stroke mask, representing stroke areas of all subjects in a single mask. After volume registration, a mean FA image was created and thinned using a threshold of 0.2 to create a mean FA skeleton, which represents the centres of all tracts common to the group. The FA skeleton mask was reduced to non-overlapping areas with the global stroke mask, which resulted in the final mask of 50.45% of the total skeleton. The average value within the skeleton was extracted for statistical analysis.

Statistics

Statistical analyses were performed in SPSS (version 22). To see if white matter integrity

related to general cognitive function, and as cognitive functions are closely linked, we used principal component analysis (PCA) to identify one global cognitive factor, but also, to test possible specific relationships, one working memory (WM) factor, with maximum 25 iterations for convergence. The variables included in the factor analyses are listed in Table 2. For MRI data at baseline raw extracted averaged FA-values were used for calculation. Correlations between FA and the cognitive factor, for both baseline and longitudinal analyses, were calculated using partial correlation controlling for movement in the scanner, age and sex. A general linear model repeated measures analysis was performed to calculate progression in trained tasks. Changes in FA in the brain mask were calculated from residuals after normalizing FA values with respect to the mean of brain stem FA values, to account for possible fluctuations in scan parameters not likely relating to the intervention. Changes in neuropsychological tests were assessed by difference in raw scores. Possible differences between pre- and post-1st and 2nd time (rest) and pre- and post 2nd and 3rd time (training), in cognitive performance as well as FA, were analysed for by paired samples t-tests.

Results

Stroke related neuropsychological characteristics

Patients with aphasia, spatial or visual neglect, homonymous hemianopia or other impairments of language or vision were not included in the study. No significant differences in cognitive performance and FA were found were found for the left (N=11) and right (N=17) hemisphere stroke group (Table 3).

As no pre-stroke measures of cognitive performance were accessible, nor were objective measures of cognitive decline as a result of stroke. However, the participants' subjective

memory performance post-stroke, in addition to scaled scores of the digit span test did not indicate training effects on cognitive function and FA. For details see Appendix.

Baseline relations between cognitive function and integrity in remaining white matter (FA)

The two factor scores, hereafter termed "cognitive factor" and "WM factor", were calculated with 19 cognitive variables and 8 isolated WM variables respectively included in the PCA (Table 2). Partial correlation revealed significant relations between both factors and FA in the global mask (cognitive factor: $r=0.60$, $p<0.01$, WM factor: 0.70, $p<0.01$), the ipsilesional hemisphere mask (cognitive factor: $r=0.57$, $p<0.01$, WM factor: $r=0.64$, $p<0.01$) and the frontal lobe mask (cognitive factor: $r=0.48$, $p=0.02$, WM factor: 0.64, $p<0.01$) at baseline, controlling for age, sex and movement in MRI scanner (Figure 1).

Mask size, relatively reflecting lesion size, correlated negatively with global FA ($r=-0.53$, $p<0.01$), the cognitive factor score ($r=-0.45$, $p=0.03$), and the WM factor ($r=-0.58$, $p<0.01$), see Table 4 for correlation among variables. When controlling for lesion size, FA did no longer correlate significantly with the cognitive factor, and vice versa, controlling for FA eliminated the relationship between lesion size and cognitive score. Controlling for hemispheric lesion side did not change the results.

Training induced changes in performance in trained computerized tasks and non-trained neuropsychological test results

Improvement was found to be significant for all four of the trained tasks, see Table 5. A paired-samples t-tests was conducted to compare the changes in non-trained WM tasks, i.e.

the WM-factor, in rest and training conditions. There was no significant difference in the change scores for the rest condition (M = -0.06, SD = 0.45) and training condition (M = 0.02, SD = 0.49); t (21) = -0.56, p = 0.58, Cohen´s d = 0.16.

Analyses on relationships between changes in cognitive function and changes in white matter microstructure (FA)

A paired samples t-test revealed no significant difference in FA-changes in rest (M = -0.003, SD = 0.44) and training (M = 0.001, SD = 0.47) conditions; t (21) = -0.02, p = 0.99, Cohen´s d = 0.004.

There were no significant correlations between changes in the WM factor and changes in global FA (r=0.128, p=0.56), frontal FA (r=0.102, p=0.64), or FA in the ipsilesional hemisphere (r=0.112, p=0.61). Using lesion size and hemispheric lesion side as regressors in correlation between WM and global, frontal and ipsilesional hemisphere respectively, did not change the relation (lesion size: r=0.062/0.054/0.038, p=0.79/0.81/0.87, lesion side: r=0.169/0.110/0.132, p=0.45/0.56/0.63).

Power

To check whether the non-significant changes in both WM-factor (d = 0.16) and FA (d = -0.004) were due to a lack of statistical power, we conducted power analyses using G*Power[47]. In order for the respective effect sizes (d) to be detected with 80 % probability and $p<0.05$, a sample of respectively 309 and 122 641 would be required to find significant changes in cognitive function and FA. Relatively large effect sizes have been reported for the relationship between cognitive training and white matter microstructure, e.g. for strategic

memory training benefit[48]. With our sample (n = 22), the analysis revealed that we had power to detect a relatively large effect size of 0.63 (two-sided), - 0.55 (one-sided).

Discussion

Can relations between cognitive function and white matter be observed in patients 1-6 years after stroke?

The results of this study support previous research connecting white matter integrity post-stroke to cognitive abilities[15,17,21]. We found a medium to strong relationship between FA and both the cognitive factor and the working memory factor, equally strong for global FA, as it was for FA in the ipsilesional and frontal part of the brain. However, our sample was highly heterogeneous in the matter of stroke type, lesion size, localization and cognitive function, and dividing the sample according to specific factors could have exposed regional differences.

Within the eligible 5 years' span in our sample, FA did not seem to be affected by the elapsed time since stroke, years of education, blood pressure, alcohol consumption or smoking. However, FA was highly correlated with lesion size. Interestingly, when controlling for lesion size FA did no longer correlate with the cognitive factor, and vice versa, controlling for FA eliminated the relationship between lesion size and cognitive score. Our findings are partly consistent with an earlier study, finding stroke volume to correlate with lower white matter intensity, but stating that lower white matter integrity was found in cognitively impaired stroke patients independently of stroke volume[15]. In another study, when controlling for stroke variables, among them stroke volume, the relationships between FA and cognitive performance even amplified, suggesting that white matter damage is independent of factors directly related to the stroke lesion[17]. However, the current study might be argumentative for

the opposite interpretation as the relationship between cognitive performance and FA seemed to be connected to the stroke volume, as well as potentially other stroke specific factors and confounding factors related to physiological and pathological processes leading up to a stroke incident.

Age was highly correlated with both white matter integrity and the cognitive factor. When controlling for age the relation between white matter characteristics (FA and lesion size) and cognitive measures was still preserved.

Can 6 weeks of training with the CCT program Cogmed QM initiate objective cognitive improvement in this patient group?

The participants improved in trained tasks corresponding to what has been shown repeatedly in previous studies[12,13,49,50]. No transfer effect was detected, which in part corresponds to, and in part is discrepant, with previous findings. Computerized, implicit working memory training has been reported to generate generalized cognitive gains for children with ADHD[51] and for adults following brain injury, including stroke[8,13,52]. However, the current absence of evidence of improvement adds to a number of studies and meta-analyses observing no transfer effect of computerized working memory training[5,53,54].

Can relationships between changes in cognitive and changes in white matter microstructure (FA) be observed?

No changes related to training were found in white matter microstructure. As no improvement was detected in the untrained tests, neither could we find any correlating or non-correlating changes in white matter integrity. In a systematic review from 2016 of computer-based

cognitive training for executive functions in stroke patients only two of twenty studies included brain parameters as measurements of effects[8]. Only one case study used DTI, in which working memory was found to fluctuate in accordance with training phases and rest phases, with corresponding changes in white matter microstructure[24].

Although the cognitive training conducted in this study did not seem to have any effect on either cognitive outcome measures other than the trained tasks or white matter integrity, longitudinal memory training studies in healthy adults have previously demonstrated positive effects on structural changes using DTI[19,22,23]. A recent study has yielded evidence that white matter integrity to some extent is predictive of the ability to benefit from cognitive training[55]. Stroke patients, with related cognitive impairment and corresponding impact on white matter microstructure, might accordingly be less likely to respond to cognitive training.

The study has limitations. The sample of participants is small, which made it challenging to divide it into subgroups (based on e.g. cognitive function, location of lesion or age). This again resulted in a relatively heterogeneous group, which might overshadow interesting subgroup differences. The profit of computerized cognitive training might differ between impaired versus non-impaired patients. The power analysis revealed that we had power to detect a relatively large effect size of with our sample, thus, we cannot rule out an effect of smaller size. However, relatively large effects of cognitive training in white matter microstructure have previously been reported in healthy adults, e.g. for strategic episodic memory training[48], and as such, the present results are disappointing. One may also argue, that for stroke patients to go through training, the expected effects should be more than minor.

In conclusion, the current study found a relationship between DTI measures and baseline cognitive functions in patients 1-6 years post-stroke, which supports white matter integrity as a biological indicator of cognitive abilities in stroke patients. No evidence was found of

generally improved cognitive function after 6 weeks of computerized cognitive training, compared to 6 passive weeks, nor were structural changes on MRI or evident correlations between the two found. With its limitations, the present study indicates questionable effects of computerized working memory training on objective memory performance in stroke patients.

Declaration of interest

The authors report no conflicts of interest.

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463 Table 1. Demographic and clinical characteristics of the sample of stroke patients included in
464 the study. BMI, body mass index; CVLT, California Verbal Learning Test; SBP, systolic
465 blood pressure; DBP, diastolic blood pressure.

	Baseline sample[1]		Training sample	
	Range (n=26)	Mean ± SD	Range (n=22)	Mean ± SD
Age	29 - 65	52.6 ± 10.3	29 – 65	51.9 ± 1.2
Months since stroke	19 - 67	41.9 ± 13.6	19 – 67	43.0 ± 13.9
IQ	88 – 130	109.7 ± 12.3	88 – 130	110.9 ± 12.8
Years of education	12 – 18	15.2 ± 2.0	12 – 18	15.3 ± 1.9
Alcohol units/ week	0 – 10	2.7 ± 3.2	0 – 9	2.4 ± 3.0
Cigarettes/ day	0 - 20	2.4 ± 6.0	0 - 20	2.4 ± 6.3
BMI	19.4 – 34.0	25.3 ± 3.5	19.4 – 34.0	24.9 ± 3.6
CVLT 30 min recall	4 - 16	10.7 ± 3.7	4 – 16	10.9 ± 4.0
SBP	102 – 178	133.6 ± 18.7	102 – 178	135 ± 19.4
DBP	62 - 113	84 ± 11.5	62 - 113	83.1 ± 12.2

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[1] The baseline sample represents the whole sample, while the training sample includes those who completed the majority of the training and are included in the longitudinal training analyses.

469 Table 2. Factor analysis computed to create 2a) a cognitive factor score from the
470 neuropsychological test battery, and 2b) a Working memory factor, based on the isolated
471 working memory tests. CVLT, California Verbal Learning Test; RCFT, Rey Complex Figure
472 Test.

473 2a

Test	Loading	Cumulative % of variance
Plus-minus test, Plus	-0.831	39.1
Letter Memory	0.822	51.9
Digit span backward	0.819	62.9
CVLT learning	0.749	72.2
Digit span forward	0.712	79.6
CVLT 30 min free recall	0.697	85.9
Plus-minus test, minus	-0.680	90.2
3 back Accuracy	0.671	93.3
2 back Accuracy	0.643	95.2
Plus-minus test, plus and minus	-0.603	96.8
Spatial working memory, total errors	-0.564	98.0
Stroop 4	-0.504	98.7
Stroop 3	-0.466	99.2
RCFT recall score		
3 back Reaction time		
2 back, Reaction time		

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475 2b

Test	Loading	Cumulative % of variance
3 back Accuracy	0.820	44.2
Digit span backward	0.809	67.9
Letter Memory	0.768	80.7
2 back Accuracy	0.763	89.1
Digit span forward	0.711	94.7
Spatial working memory, total errors	-0.659	97.7
3 back Reaction time		
2 back, Reaction time		

476 Table 3. Comparison of clinical factors between patients with left and right hemispheric
477 stroke. FA, fractional anisotropy; WM factor, working memory factor; SBP, systolic blood
478 pressure; DBP, diastolic blood pressure
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	Left hemispheric stroke (11)	Right hemispheric stroke (17)	Difference between groups
	Mean (SD)	Mean (SD)	Sig., p
Age	49.5	54.3	0.38
Global FA	0.44548 (0.20079)	0.46040 (0.02637)	0.20
Cognitive factor	-0.29 (1.43)	0.15 (0.59)	0.45
WM factor	-0.20 (1.44)	0.06 (0.67)	0.60
Lesion size	29689 (26922)	42386 (47673)	0.51
IQ	110 (13)	108 (12)	0.71
SBP	127 (20)	140 (23)	0.24
DBP	81 (10)	88 (14)	0.36

Table 4. Baseline correlations of white matter and cognitive function with demographic and clinical variables. FA, fractional anisotropy; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Baseline correlations[2]		
	FA	Cognitive factor
	Correlation (p)	Correlation (p)
Cognitive factor	0.600 ***(0.01)***	
Age	-0.459 ***(0.02)***	-0.422 ***(0.04)***
IQ	0.470 ***(0.02)***	0.699 ***(0.01)***
Matrix	0.418 ***(0.05)***	0.487 ***(0.02)***
Vocabulary	0.393 (0.06)	0.687 ***(0.01)***
Months since stroke	-0.005 (0.98)	0.089 (0.69)
Years of education	-0.020 (0.93)	0.162 (0.46)
Cigarettes per day	-0.242 (0.27)	-0.26 (0.24)
Alcohol units per week	-0.161 (0.46)	0.043 (0.85)
BMI	-0.009 (0.97)	0.169 (0.44)
SBP	-0.191 (0.38)	0.087 (0.69)
DBP	-0.364 (0.09)	-0.210 (0.34)
Lesion size	-0.533 ***(0.01)***	-0.447 ***(0.03)***

[2] Correlations were controlled for movement in scanner, age and sex.

501 Table 5. Training induced changes in the trained tasks using a general linear model repeated

502 measures analysis.

	Day 3 of training		Second to last day of training			Correlation to changes in global FA
	Mean	SD	Mean	SD	Significance	R (p)
Grid[3]	5.25	0.69	6.23	1.47	***0.01***	0.259 (0.23)
Numbers	5.97	1.61	7.56	2.61	***0.01***	-0.066 (0.77)
Cube	4.56	0.59	5.30	0.76	***0.01***	0.284 (0.19)
Hidden numbers	5.21	1.48	7.08	2.60	***0.01***	-0.072 (0.74)

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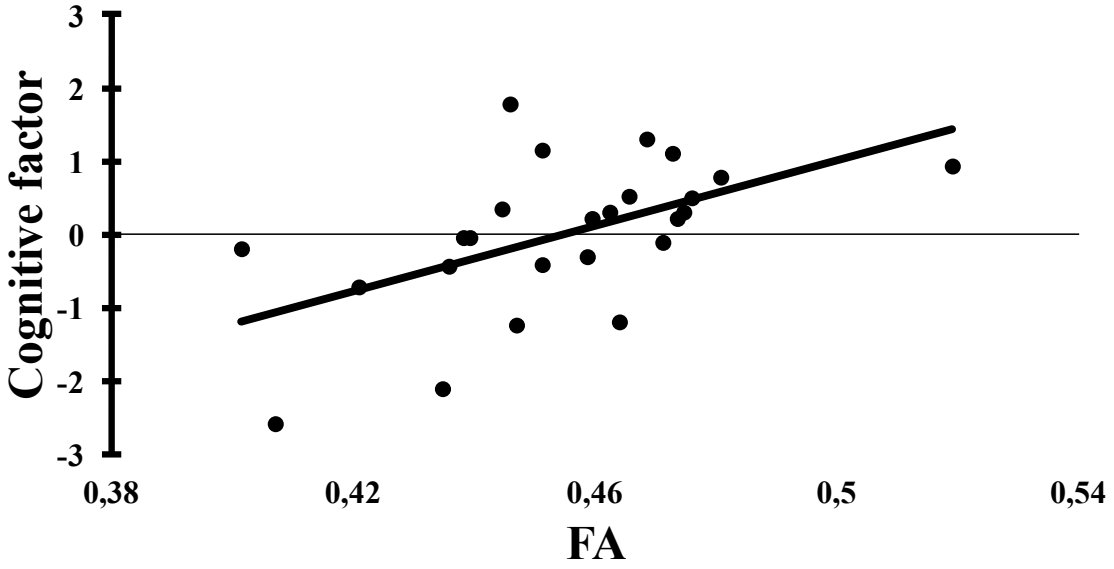
[3] Four of the trained exercises in Cogmed QM were used for calculation of improvement in trained tasks, as they were presented at all training days. The metrics of improvement in trained tasks were done for those completing at least 90% of the training days (minimum 22/25 days, n=20).

Figure 1. The association between 1a) cognitive function (cognitive factor) and 1b) working memory (WM factor) and white matter (FA) at baseline. The relationship was significant with a correlation of $r = 0.60$, $p < 0.01$ and $r = 0.70$, $p < 0.01$ respectively.

1a)



1b)