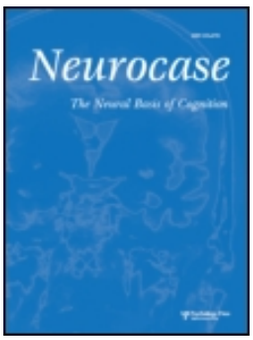

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Exploring the relationship between white matter microstructure and working memory functioning following stroke: A single case study of computerized cognitive training

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Cognitive impairment is a well-known consequence of acquired brain injuries, including stroke. Computerized cognitive training (CCT) is a rehabilitation approach intended to enhance cognitive functioning. It is unclear whether CCT leads to generalized cognitive improvements in daily life functioning, or if the subjects improve performance only on the exercises involved in the training. The current study explores whether fractional anisotropy (FA), a measure of white matter microstructure, may serve as an indirect biological indicator of enhanced neuropsychological functioning, particularly working memory, following CCT. The findings suggest a possible relationship between changes in FA measures and working memory.

Keywords: Cognitive rehabilitation; Computerized cognitive training; Stroke; Diffusion tensor imaging; Fractional anisotropy.

Recent knowledge about neural plasticity has led to increased optimism regarding the brain's ability to adapt to new conditions – not only in the early years of life, but throughout lifespan (Buonomano & Merzenich, 1998; DeFelipe, 2006; Draganski, Gaser, Busch, Schuierer, Bogdahn, & May, 2004; Draganski & May, 2008; Jones, Nyberg, Sandblom, Neely, Ingvar, Petersson, et al., 2006). In parallel, advances in information and communication technology have provided opportunities for exercise-based rehabilitation systems characterized by being individually customizable, user-friendly, highly systematic in monitoring progress, and reinforcing of task-adaptive behavior. In the 1980s when the first computerized cognitive training (CCT) software was put in to use, the results were discouraging for patients with traumatic brain injury in the sense that computer-based intervention showed little effect beyond that of standard treatment (Ponsford & Kinsella, 1988). Later, in a review of cognitive rehabilitation of acquired brain injury (ABI) examining studies published before year 2000, Cicerone and colleagues concluded that 'computer-based interventions may be used within a multi-modal intervention for cognitive deficits, as long as a therapist is actively involved to foster insight into cognitive strengths and weaknesses, to develop compensatory strategies, and to facilitate the transfer of skills from the treatment tasks to real-life situations' (Cicerone, Dahlberg, Kalmar, Langenbahn, Malec, Bergquist, et al., 2000, p. 1607). In the review, the authors

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identified only two studies meeting a satisfactory methodological standard (Batchelor, Shores, Marosszeky, Sandanam, & Lovarini, 1988; Chen, Thomas, Glueckauf, & Bracy, 1997). The two studies compared computerized cognitive rehabilitation to non-computerized neuropsychological rehabilitation, and reported significant post-rehabilitation improvements on neuropsychological measures for both the CCT groups and the comparisons. No significant between-group differences were found. These findings indicate, as Ponsford and Kinsella (1988) found, that CCT does not improve cognitive functioning more than other kinds of neuropsychological rehabilitation. Still, CCT had a significant effect on post-training measures, and, as Chen and colleagues concluded, there may be both clinical and economic reasons for offering home-based CCT as an alternative or supplement to other types of neuropsychological rehabilitation.

This perspective was advocated in a more recent study in which the effects of a computer-assisted, a tele-medical and a face-to-face version of the same problem-solving program for persons with ABI were tested (Man, Soong, Tam, & Hui-Chan, 2006). The findings showed comparable significant improvement for the three treatment conditions, while the control group (no treatment) showed no significant change. Similarly, a study contrasting computerized cognitive training with a passive control group found an advantage effect of CCT in a sample of chronic stroke patients (Westerberg, Jacobaeus, Hirvikoski, Clevberger, Ostensson, Bartfai, et al., 2007). The findings of these studies indicate that there seems to be a positive effect of CCT, but the effect does not necessarily extend beyond the effect of non-computerized cognitive training. It remains undecided whether this is mainly due to a general effect of neuropsychological rehabilitation, or specific effects (similar in strength) associated with specific types of cognitive rehabilitation. Additionally, it is not known whether CCT truly enhances cognitive performance, or if the improvement merely indicates that the subjects have become better in performing neuropsychological tests that resemble the computer exercises, as suggested in a recent study involving patients diagnosed with schizophrenia (Dickinson, Tenhula, Morris, Brown, Peer, Spencer, et al., 2010).

An approach that might clarify possible mechanisms behind the improvement found in some CCT studies is the identification of biological indicators of training effect (Klingberg, 2010; Klingberg & McNab, 2009; McNab, Varrone, Farde, Jucaite, Bystritsky, Forssberg, et al., 2009). Changes in grey matter volume have been shown to be an effect of acquiring a new motor skill (Draganski et al., 2004; Driemeyer, Boyke, Gaser, Buchel, & May, 2008), as well as training with mnemonic techniques (Engvig, Fjell, Westlye, Moberget, Sundseth, Larsen, et al., 2010), intensive studies (Draganski, Gaser, Kempermann, Kuhn, Winkler, Buchel, et al., 2006) and practice of a computerized spatial task (Haier, Karama, Leyba, & Jung, 2009). These findings suggest that the brain is capable of continuously adapting to new conditions, also at a structural level. In CCT the object of training is the overall capacity in one or several domains of cognitive functioning. All cognitive functions depend on a network of distinct brain regions, rather than one specific area. Thus, changes in white matter microstructure may be a more sensitive measure of the effect of CCT than grey matter volume.

In recent years, diffusion tensor imaging (DTI) has emerged as a method for studying white matter microstructure *in vivo*. By measuring water molecule displacements impeded by different tissue elements, microstructural characteristics are inferred (Beaulieu, 2002; Le Bihan, 2003). Fractional anisotropy (FA) indicates degree of directional coherence of water displacements (Pierpaoli & Basser, 1996), and changes in FA and other DTI measures may indicate changes in the structural features of neural tissue, for instance due to pathology (Alexander, Lee, Lazar, & Field, 2007). FA has been found to decrease in both ipsilateral and contralateral hemispheres following stroke (Buffon, Molko, Herve, Porcher, Denghien, Pappata, et al., 2005). For the contralateral hemisphere there was a significant drop in FA between 3 and 6 months after the incident. However, little is known about how white matter microstructures may or may not be influenced by cognitive rehabilitation. This is of great interest, especially since a number of studies have indicated considerable plasticity of white matter microstructure, including activity-dependent change in myelination (Fields, 2008) and FA (Scholz, Klein, Behrens, & Johansen-Berg, 2009). Animal studies have indeed shown that very rapid, even seasonal, changes in FA can occur with varying behavior (De Groof, Verhoye, Poirier, Leemans, Eens, Darras, et al., 2009; De Groof, Verhoye, Van Meir, Balthazart, & Van der Linden, 2008). A recent study found increases in FA in traumatic brain injury patients across one year post trauma, particularly with

favorable outcome (Sidaros, Engberg, Sidaros, Liptrot, Herning, Petersen, et al., 2008). As for cognitive rehabilitation, very scarce data exist, but one recent study using DTI found significant increase in number of fibers in right arcuate fasciculus in patients with Broca's aphasia undergoing speech therapy (Schlaug, Marchina, & Norton, 2009). This suggests that DTI may serve as a valuable neural marker of training-induced changes.

The aim of this study was to explore whether a white matter microstructure measure, FA, may serve as a biological basis of enhanced working memory functioning following computerized cognitive training.

Three research questions were investigated:

1. Does neuropsychological performance, especially working memory, fluctuate with CCT provided following stroke?
2. What is the course of white matter (FA) change in brain areas not directly affected by the stroke?
3. Are there corresponding changes in FA and neuropsychological performance, especially on working memory tasks?

METHOD

Case history

LE is a right-handed male who at the time of suffering a right hemisphere stroke was 60 years old. He was hospitalized with suspicion of right hemisphere infarct due to acute left-sided numbness, slurred speech, headaches and difficulty with visual focus. Hours after hospitalization his condition became worse, and he was increasingly somnolent. A CT scan showed major right temporal hemisphere intracerebral and intraventricular bleedings. After four days of neurological observation and conservative treatment, there was respiratory worsening and he received Continuous Positive Airway Pressure (C-PAP) and was medicated for possible aspiration pneumonia. For these symptoms he received respiratory treatment for 12 days. He showed some circulatory instability and arterial flutter, and had a Glasgow Coma Scale (GCS) score of 10 when a craniotomy was performed and a hematoma was evacuated. After this he was awake and relatively alert with a GCS of 14–15. All in all, he received treatment to stabilize his medical condition for 17 days before he was transferred to a rehabilitation ward at a local hospital (admitted for 49 days) and later to a rehabilitation center where he stayed for 30 days. At the local hospital and the rehabilitation center he received further medical care and information about stroke and how it may affect his life, in addition to physiotherapy and occupational therapy, but no CCT. Three months and three weeks after the stroke he was admitted to a cognitive rehabilitation unit at Sunnaas Rehabilitation Hospital (SRH) where he volunteered to participate in this study. In the first study phase (T0–T1; 4.5 to about 7.5 months post stroke), the subject received standard treatment including neuropsychological assessment, occupational therapy and physical training at the cognitive rehabilitation unit. Apart from the treatment offered at SRH and in this study, he did not receive any cognitive rehabilitation for his cognitive impairment, a situation which is quite common for stroke patients in Norway. Prior to the stroke, the patient was working full-time as a lawyer (19 years of education). He had hypertension, and post-stroke he described episodes of palpitation before the incident. Later he was diagnosed with arrhythmia. A family history of increased chance of heart disease is reported in his medical charts but not otherwise specified. He had no prior history of stroke, seizure, CNS infections, traumatic brain injury, concussion, or loss of consciousness. The severity of the cognitive impairments following the stroke has prevented him from resuming his work, but he is living at home with his spouse and is able to carry on most daily life activities. He has been highly motivated for intensive cognitive training all through the study.

Neuroradiological findings

A specialist in neuroradiology evaluated LE's T1-weighted, T2-weighted and coronal SPACE (*S*ampling *P*erfection with *A*pplication-optimized *C*ontrasts by using different flip angle *E*volutions) MRI scans. There were postoperative changes in the right cranium and major sequelae in the form of substance loss in a large part of the lateral right posterior temporoparietooccipital area with signal changes in adjacent tissue (Figure 1). A cystic change in the anterior part of the middle temporal lobe was found, also with sequelae in the form of high intensity signal changes in adjacent tissue. There was a secondary retraction of the temporal horn which was dilated, and there was also a dilation of the right lateral ventricle. Other parts of the brain were deemed normal, including the brain stem, corpus callosum and cerebellum.

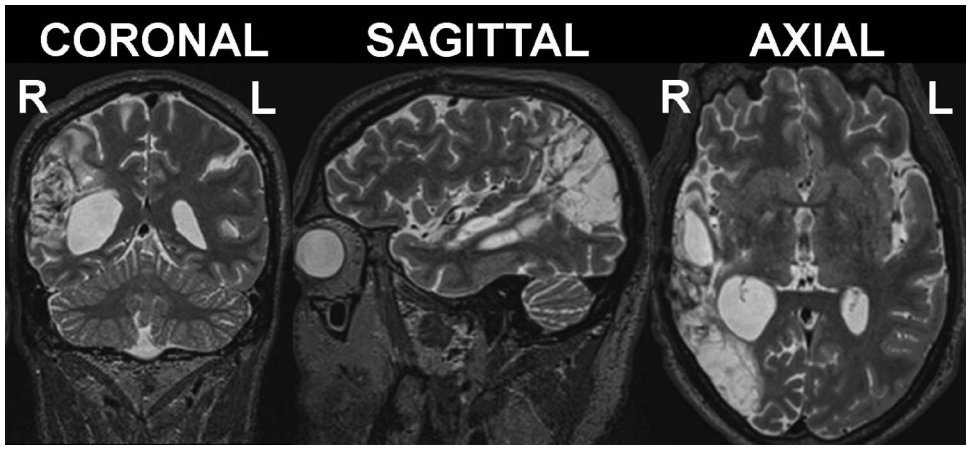

Figure 1. MRI displays of brain areas affected by the stroke.

Neuropsychological assessment

To monitor changes in cognitive functioning, we chose neuropsychological measures commonly used in clinical evaluation of cognitive impairments: Wechsler Memory Scale III (selected subtest; Wechsler, 1997), Delis-Kaplan Executive Function System (selected subtest; Delis, Kaplan, & Kramer, 2001) and Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). In addition, Paced Auditory Serial Addition Test (PASAT, 2 sec.version, Norwegian edition; Landro, Celius, & Sletvold, 2004) was included to provide a measure recognized to target impaired updating and central executive processes of working memory following brain injury (Vakil, 2005). The neuropsychological tests were organized in six areas of cognitive function: Working memory (Letter-number seq., Spatial Span – Backward, Digit Span – Backward and PASAT), immediate recall (Verbal Pair Association I, Visual Reproduction I, Logic memory I, Faces I, Family Pictures I and Word List I), delayed recall (Verbal Pair Association II, Visual Reproduction II, Logic memory II, Faces II, Family Pictures II and Word List II), executive functions (STROOP – 3, STROOP – 4 and Tower Test), general cognitive abilities (WASI) and psychomotor speed (TMT – 5, STROOP – 1 and STROOP – 2). The subject was assessed on the same neuropsychological tests six times, from T0 to T5, at the beginning of each phase. Table 1 shows raw score and s-score at T0 (baseline; 4.5 months post injury) and at T5 (final re-assessment; 22 months post injury).

Cognitive training

Two different training software systems were used in this study. The initial one (NeuropsychOnline.com) was selected because, at the time of the planning of this study, it was one of the few mentioned in the literature on brain injury rehabilitation (Cicerone et al., 2000). As the study developed and the neuropsychological measures indicated that working memory was a core area of impairment, CogMed QM, a clinical working memory training software, was chosen to target that particular difficulty. The *NeuropsychOnline.com* is the updated, Internet-based version of the PSSCogRehab System (Chen et al., 1997). In this study, excercises from five different areas of cognition were selected: Visuospatial skills, attention, memory, executive functions (focusing on abstract categorization) and problem solving. This CCT system is organized hierarchically, starting with simple tasks and evolving to more difficult exercises. The cognitive training was organized as individual training (home-based) three to four times a week (60 min per session), plus one weekly session with a clinical psychologist. These weekly sessions focused on developing cognitive strategies, educational perspectives on cognition, and motivational factors. *CogMed QM* is the adult version of the CogMed training software. It was developed to enhance working memory performance, and has in particular been tested with children diagnosed with ADHD (Klingberg, 2007; Klingberg, Fernell, Olesen, Johnson, Gustafsson, Dahlstrom, et al.,

TABLE 1
Neuropsychological assessment

		T0 – Baseline 4.5 months post injury		*T5 – Final test 22 months post injury*	
		Raw score	*S-score*	*Raw score*	*S-score*
Working memory			**5,3**		**9,8**
Letter-number seq	WMS III	5	5	12	13
Spatial Span – Backward	WMS III	2	3	6	9
Digit Span – Backward	WMS III	6	10	6	10
PASAT		21	3	43	7
Immediate recall			**11,0**		**14,3**
Verbal Pair Association I	WMS III	30	16	32	17
Visual Reproduction I	WMS III	58	6	55	11
Logic memory I	WMS III	43	12	65	18
Faces I	WMS III	39	13	44	17
Family Pictures I	WMS III	22	5	44	11
Word List I	WMS III	36	14	45	18
Delayed recall			**11,2**		**13,5**
Verbal Pair Association II	WMS III	8	14	8	14
Visual Reproduction II	WMS III	55	5	58	6
Logic memory II	WMS III	30	14	43	17
Faces II	WMS III	35	10	43	17
Family Pictures II	WMS III	17	5	42	11
Word List II	WMS III	8	13	11	16
Executive functions			**7,0**		**11,0**
STROOP – 3	D-KEFS	71	10	53	13
STROOP – 4	D-KEFS	160	1	79	10
Tower Test	D-KEFS	15	10	16	10
WASI			**9,5**		**11,8**
Similarities	WASI	42	14	39	13
Vocabulary	WASI	72	15	77	16
Matrix Reasoning	WASI	9	5	17	9
Block Design	WASI	4	4	28	9
Psychomotor speed			**9,7**		**9,3**
TMT – 5	D-KEFS	26	12	23	13
STROOP – 1	D-KEFS	36	9	37	8
STROOP – 2	D-KEFS	29	8	31	7

2005). All in all, it consists of 11 different exercises; however, a training session involves only eight of these. In a normal training course, there are 25 sessions of about 35–45 min each. In the beginning of a session, one of eight tasks is chosen to work with, until the software automatically takes the person to the next task. The software guidelines recommend that the training to be finished in 5 weeks, completing one session each weekday. As for other cognitive training software, some of the exercises appear to be inspired by neuropsychological tests. For more details, see Westerberg and colleagues (2007). For the current study, an ABABC design was chosen (A=No cognitive training; B=Cognitive training with NeuropsychOnline.com; and C= Cognitive training with CogMed QM).

MRI acquisition

Imaging data were acquired using a 1.5 T Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany) with a 12-channel head coil. For the neuroradiological evaluation, two T2-weighted pulse sequences were used: Fluid-attenuated inversion-recovery (FLAIR), and sampling perfection with application-optimized contrasts by using different flip angle evolutions (SPACE). The parameters for the FLAIR sequence were as follows: Repetition time (TR) = 9000 ms, echo time (TE) = 109 ms, inversion time (TI) = 2500 ms, flip angle = 150°, matrix 448 × 512, field of view (FOV) = 448, voxel size 0.45 × 0.45 × 6.50 mm, 26 coronal slices. Scanning time was ~4 min. For the SPACE sequence, these

parameters were used: TR = 3390 ms, TE = 388 ms, TI = −1.0 ms, flip angle = 120°, matrix 204 × 256, FOV = 204, voxel size 1.0 × 1.0 × 1.0 mm, 176 sagittal slices. Scanning time was 5 min. Diffusion-weighted images were acquired using a single-shot twice-refocused spin-echo echo-planar imaging pulse sequence with 30 diffusion sensitized gradient directions and the following parameters: TR = 8200 ms, TE = 82 ms, b-value = 700 s/mm^2, voxel size = 2.0 × 2.0 × 2.0 mm, 64 axial slices. The sequence was repeated in two successive runs with 30 diffusion-weighted and 10 b = 0 volumes collected per acquisition. Total scanning time was ∼11 min. This sequence is optimized to minimize eddy current-induced image distortions (Reese, Heid, Weisskoff, & Wedeen, 2003). The two acquisitions were averaged during post-processing to increase the signal-to-noise ratio (SNR).

DTI analysis

Diffusion data were analysed using tools in FSL 4.1.2 (www.fmrib.ox.ac.uk/fsl) (Smith, Jenkinson, Woolrich, Beckmann, Behrens, Johansen-Berg, et al., 2004; Woolrich, Jbabdi, Patenaude, Chappell, Makni, Behrens, et al., 2009). In creating the white matter skeleton (see below), scans from a group of controls from an independent study were also used to ensure that the white matter voxels studied were common to multiple persons (n = 19; age range 53–70, mean= 62.6, SD = 50.1; gender: All male). First, each DTI volume was affine registered to the T2 weighted b = 0 volume using FLIRT (Jenkinson & Smith, 2001), correcting for motion between scans and residual eddy current distortions in the diffusion-weighted images. After averaging the two acquisitions, diffusion tensors were fitted at each voxel and served to create the FA maps. Next, all FA volumes were skeletonised and transformed into a common space using Tract-Based Spatial Statistics (TBSS) (Smith, Jenkinson, Johansen-Berg, Rueckert, Nichols, Mackay, et al., 2006; Smith, Johansen-Berg, Jenkinson, Rueckert, Nichols, Miller, et al., 2007). Briefly, all volumes were nonlinearly warped to the FMRIB58_FA template (www.fmrib.ox.ac.uk/fsl/data/FMRIB58_FA.html) using local deformation procedures performed by FNIRT (Andersson, Jenkinson, & Smith, 2007a, 2007b), a non-linear registration tool employing a b-spline representation of the registration warp field (Rueckert, Sonoda, Hayes, Hill, Leach, & Hawkes, 1999). We visually inspected all warped FA volumes for accuracy, which is especially pertinent when analyzing brains with gross lesions (Smith et al., 2006). Specifically, inaccurate warping may occur when structures are present in the standard, but not the native, brain. To account for this discrepancy due to gross lesions, we drew a mask in the patient's initial volume corresponding to the areas lesioned by the stroke, and employed this to cover areas showing signal attenuation in the diffusion-weighted and b = 0 volumes, effectively masking out the lesioned areas. Thus, the native-to-standard warping was based on only structures present in both native and standard spaces, and warping accuracy was judged satisfactory.

Next, a mean FA volume of all subjects was created and thinned to generate a mean FA skeleton, representing the centres of all common tracts. We thresholded and binarized the mean skeleton at FA > 0.25 to reduce the likelihood of partial voluming in the borders between tissue classes. These procedures yielded a skeleton mask for the anterior left (22 135 voxels), anterior right (22,633 voxels), and posterior left (31,920 voxels) parts of the skeleton (see below) of 76,688 white matter voxels. Individual FA values were projected onto the mean skeleton mask by searching perpendicular to the skeleton for maximum values in each subject's FA image. Using maximum FA values from the centers of the tracts further minimizes confounding effects due to partial voluming (Smith et al., 2006). The resulting tract-invariant skeletons for LE's six different time points were used to explore differences in FA. Finally, a frontal lobe mask from the MNI structural atlas (Collins, Holmes, Peters, & Evans, 1995; Mazziotta, Toga, Evans, Fox, Lancaster, Zilles, et al., 2001), part of FSL, was used to create a frontal WM mask, with additional manual intervention consisting of filling in underlying white matter. The posterior white matter mask was defined as the remaining part of the left hemisphere; the two masks thus covered skeleton voxels anterior and posterior to the central sulcus, respectively (see Figure 2 for mask renderings). We wished to investigate whether white matter microstructure in non-injured brain areas would fluctuate with training. Recent studies have reported an association between white matter microstructure and working memory for the whole brain, sub-regions and specific fiber tracts

(Charlton, Barrick, Lawes, Markus, & Morris, 2010; Dineen, Vilisaar, Hlinka, Bradshaw, Morgan, Constantinescu, et al., 2009; Ewing-Cobbs, Prasad, Swank, Kramer, Cox, Fletcher, et al., 2008; Nestor, Kubicki, Nakamura, Niznikiewicz, McCarley, & Shenton, 2010; Schiavone, Charlton, Barrick, Morris, & Markus, 2009; Williamson, Nyenhuis, Stebbins, Lamb, Simkus, Sripathirathan, et al., 2010). Since the right temporoparietooccipital area was affected by the stroke, we decided to target other areas of the brain, and divided the DTI mask into a right anterior (frontal) section, a left anterior section and, finally, a left posterior section. This subdivision enabled a comparison across both hemispheres (right frontal and left frontal) and anterior versus posterior (left anterior vs. left posterior). Working memory has in particular been associated with activation in the prefrontal cortex, but other brain regions have been linked to working memory performance as well (D'Esposito, 2007), including, importantly, posterior parietal areas (Berryhill & Olson, 2008). Due to the single-case design of the present study, we decided not to analyze further multiple smaller areas of interest, but rather focus on frontal versus posterior regions. We were concerned with the relative changes over time in FA between the three areas mentioned above, where we expected a possible effect of cognitive training. To reduce the influence of scanning-related noise between scans, including any drift in time in the scanner diffusion gradients, FA in all ROIs were divided by FA in a mask drawn in the brain stem (Figure 2), an area likely to be unaffected by training. The brain stem mask was taken from the Harvard-Oxford subcortical structural atlas, also a part of FSL, and thresholded at 0.95.

RESULTS

Does neuropsychological performance, especially working memory tasks, fluctuate with CCT provided following stroke?

All cognitive functions, apart from working memory, showed normal to high achievement from T0 to T5 (Figure 3A). The general trend was an increase in performance across all intervals, apparently largely irrespective of training/no training.

Working memory stood out from the others; the results at T1 were not better than at T0, indicating no apparent test–retest effects or spontaneous recovery for working memory performance. Further, the WM results appeared to be shifting with the training phases.

What is the course of white matter (FA) change in brain areas not directly affected by the stroke?

Table 2 shows raw FA scores for anterior right hemisphere, anterior left hemisphere, posterior left hemisphere and the brain stem. As shown in Figure 3B, for the first 3 months of no training there appeared to be a fall for all three FA ratio measures. Thereafter a slight increase was observed for the next 3.5 months of training, and then stagnation or minor decline in the no training period which followed (3 months). For the next two blocks of training (2×4 months), a relatively larger increase in anterior-posterior FA was observed in the first phase, followed by a smaller increase in the final training phase.

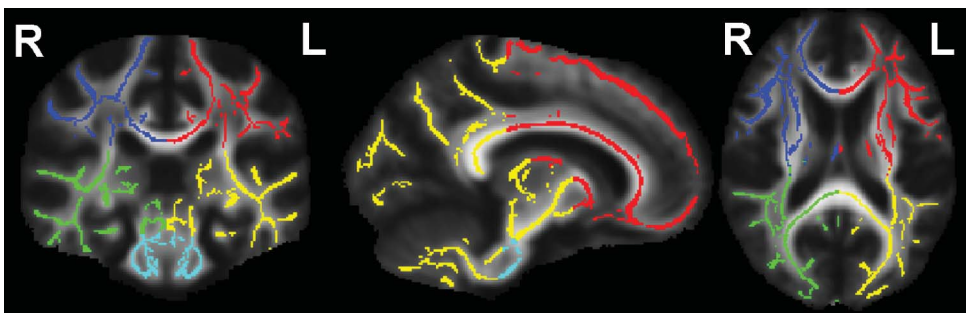

Figure 2. matter tracts skeleton. Dark blue = right frontal, green = right posterior, red = left frontal, yellow = left posterior and light blue = brain stem. [To view this figure in color, please visit the online version of this Journal.]

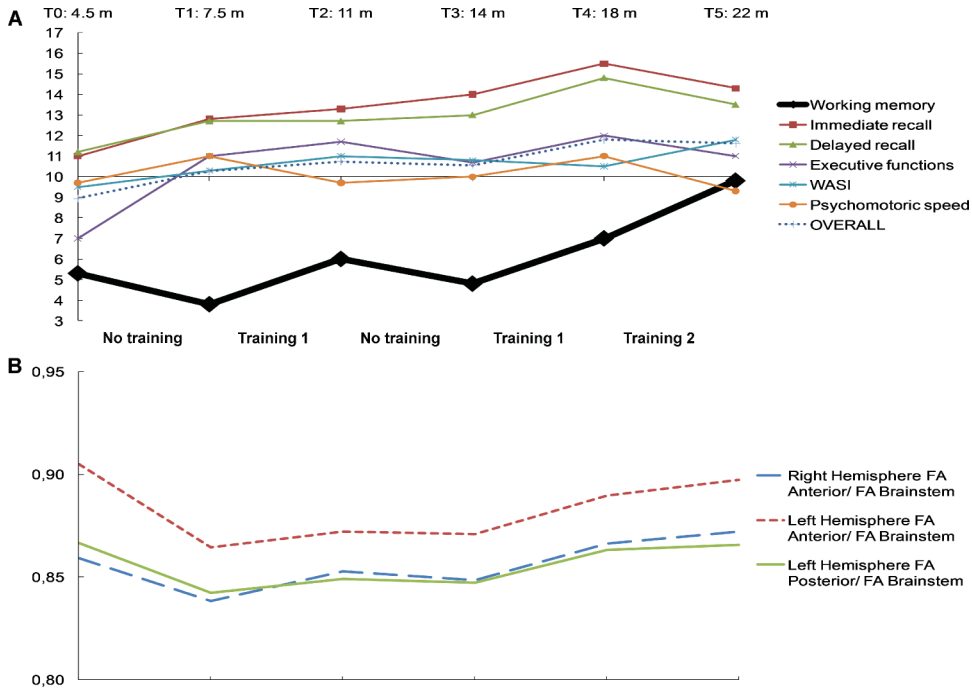

Figure 3. (A, B) The top line diagram shows neuropsychological test results (s-scores), overall score and split by the six cognitive domains. The bottom line diagram shows changes in the ratio of FA in the three target areas and the brain stem. [To view this figure in color, please visit the online version of this Journal.]

TABLE 2
FA values

	Right frontal	*Left frontal*	*Left posterior*	*Brain stem*
T0	0.4766	0.5020	0.4806	0.5546
T1	0.4890	0.5043	0.4914	0.5834
T2	0.4735	0.4843	0.4714	0.5554
T3	0.4853	0.4981	0.4849	0.5720
T4	0.4914	0.5048	0.4896	0.5673
T5	0.4827	0.4965	0.4790	0.5534

Are there corresponding changes in neuropsychological performance, especially working memory and FA?

For LE, no drop in absolute FA was apparent for the initial 3 months of no training. However, a fall in FA ratio scores appeared to be the case (see above). This may be part of tissue changes following stroke as previously reported (Buffon et al., 2005). For the same phase, there appeared to be a drop in working memory capacity. Figure 4 shows scatterplots for the three FA ratio scores and working memory. The correlation was fairly high between all FA ratio scores and working memory (varying from r=.58 to r=.91), but only the relationship between anterior right hemisphere FA/brain stem FA ratio and working memory was significant (r=.91, p=.013), explaining 83% of the variance in this time interval of training and no training.

DISCUSSION

Does neuropsychological performance, especially working memory, fluctuate with CCT provided following stroke?

The results suggest that the patient improved his performance in 5 out of 6 cognitive domains (working memory, immediate and delayed recall, executive and general cognitive functions, but not psychomotor speed) during the study phase of approximately 18 months. Some degree of behavioral spontaneous recovery is expected after suffering a stroke (Cramer, 2008). Additionally, practice effects probably boosted the neuropsychological test scores (Dikmen, Heaton, Grant, & Temkin,

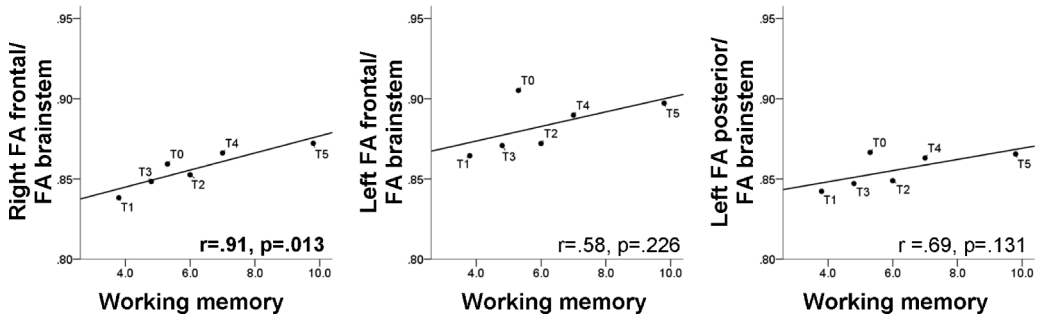

Figure 4. Scatterplots of the relationships between FA right frontal, FA left frontal and FA left posterior; and working memory.

1999). Still, after the initial phase of recovery in the no training phase (4.5–7.5 months), the overall results tend to show a slight fluctuation with the no training/training phases. This may indicate an effect of cognitive training, which appears primarily for working memory. The working memory score consequently drops after 'No training' phases and increases after CCT phases. The other neuropsychological measures do not show the same pattern (Figure 3A). One previous study has shown stable neuropsychological development in most cognitive domains for a year after suffering a stroke, apart from significant decrease in verbal memory and visuoconstructive performance and a trend towards significant decline for working memory (Sachdev, Brodaty, Valenzuela, Lorentz, & Koschera, 2004). Further, stroke increases the probability of developing mild cognitive impairment and vascular dementia (Sachdev, Chen, Brodaty, Thompson, Altendorf, & Wen, 2009). Hence, long-term improvements in cognitive functioning are not a typical outcome after stroke. Moreover, if the observed cognitive improvements only were due to treatment-unrelated factors, i.e., spontaneous recovery and test practice effects, it seems reasonable to assume a stable progression across cognitive domains. Since this is not the case, it is possible that working memory is more sensitive to CCT than other cognitive functions. However, the design of the current study is not especially suited to determine this matter.

The current study employed two different types of CCT software, the initial type targeting five various areas of cognitive functioning and the other focusing on working memory. Their effects on cognitive measures do not seem to be very different. Future research may elucidate whether cognitive training has a general effect on working memory – an effect less dependent on the content of the training. If this is the case, it would explain why different rehabilitation programs may have similar outcomes (e.g., Man et al., 2006).

What is the course of white matter (FA) change in brain areas not directly affected in the post-stroke phase?

FA tissue changes following stroke with decreases in FA from 3 to 6 months post incident have been previously reported (Buffon et al., 2005), but for the present patient, absolute decline in FA values in the initial phase was not observed. However, such changes may have taken place in the first 4.5 months prior to the first scan in the present study. There was still some indication of white matter microstructural changes during the current scan intervals, in terms of changes in the ratio between FA in the three target regions and brain stem FA. For the first 3 months (4.5–7.5 months post stroke) of no training, a steep fall in anterior-posterior FA appeared. Thereafter a slight increase was observed for the next 6.5 months of training (3.5 months) and no training (3 months). For the next two blocks of training (2 × 4 months), a relatively larger increase in anterior–posterior FA was observed. This FA estimate has the advantage of evening out possible small fluctuations in FA due to different positioning in the scanner and other small scan variations with time (see, e.g., Cercignani, Bammer, Sormani, Fazekas, & Filippi, 2003). To our knowledge, no studies showing how FA develops beyond 6 months after the incident are available. Thus, the normal course of development of FA in the post-stroke phase is not known, and future studies evaluating the effect of cognitive training for stroke patients would highly benefit from such knowledge.

Are there corresponding changes in neuropsychological performance, especially working memory, and FA?

For most neuropsychological measures there was a slight but steady improvement throughout the period of the study, but this did not seem to correspond directly to changes in the FA ratio scores. Thus, the current study does not show strong evidence of a direct relationship between general neuropsychological functioning and white matter microstructure across training phases. However, working memory stood out from this general pattern as a function that varied with both training phases and white matter microstructure changes. For the initial phase of no training (4.5–7.5 months post stroke), there appeared to be a drop in working memory capacity as well as FA in all three ROIs. Thereafter, working memory seems to be declining after periods of no training and increasing after training. The correlation of right hemisphere anterior FA with working memory was highly significant. For the left hemisphere FA, the T0 tests stand out with a high FA ratio score and low working memory score (Figure 2). The data are not clear, but possibly decline in contralateral FA happens with a slower pace than for ipsilateral FA, while the effect of the stroke on working memory is immediate.

Limitations and implications for further research

We studied a patient with a posterior right hemisphere stroke and consequent neuropsychological impairment including verbal and visuospatial working memory problems. One may question to what extent the problems seen in this patient, and his recovery, can be representative also of other lesions, e.g., left hemisphere infarcts, or even of other similar right hemisphere lesion cases. As mentioned, right hemisphere DTI changes have been observed in left hemisphere stroke patients undergoing speech therapy (Schlaug et al., 2009). Recovery of motor skill in left and right hemisphere stroke patients has also been linked to FA in both ipsilesional and contralesional corticospinal tract (Schaechter, Fricker, Perdue, Helmer, Vangel, Greve, et al., 2009). However, we are not aware of other DTI studies of right hemisphere stroke patients in cognitive rehabilitation besides this one. While it is known that the right posterior parietal cortex is critical to visual working memory (e.g., Berryhill & Olson, 2008), one may question whether broader working memory problems, including verbal tasks, may be typical after right hemisphere lesions. The left inferior parietal cortex has been claimed to be the site of a phonological short-term store (Muller & Knight, 2006), but fMRI studies show bilateral parietal activation in verbal working memory tasks (e.g., D'Esposito, 2007). The right parietal involvement can be attributed either to a spatial processing component in verbal working memory tasks (e.g., Ravizza, Behrmann, & Fiez, 2005), or broader functions involving attention known to activate overlapping bilateral brain areas as working memory tasks, including verbal ones (LaBar, Gitelman, Parrish, & Mesulam, 1999). Regardless of degree of specificity of the mechanism involved, working memory problems also involving verbal tasks have been reported to result from right hemisphere lesions also by others (Ravizza et al., 2005).

The observed changes in FA across no training and training phases were, as described above, not absolute FA scores, but normalized scores achieved by dividing FA from brain areas possibly influenced by the training with FA from an area believed not to be affected by training (the brain stem). In a single subject study, unsystematic error is a larger threat to the study than in group designs. Normalizing the scores may help neutralize error variance across scans. However, to investigate whether the observed fluctuations represent true changes in FA values, the matter needs to be addressed in a randomized controlled trial. Such a design might also determine if similar changes occur in a larger sample of stroke patients.

Since the first scan was performed 4.5 months post incident, we do not know how FA changes in the first period of time after the stroke. While some recovery of functioning is commonly observed in the weeks following a stroke (Cramer, 2008), in parallel, a decrease in FA may be taking place during the first months post-stroke (Buffon et al., 2005). To achieve a better understanding of post-stroke white matter and cognitive changes, it would be important to perform scans closer in time to the incident.

The findings of the current study suggest that FA may serve as a biological marker of cognitive training relevant changes in working memory performance post stroke. The nature of the relationship between FA scores and working memory remains unclear, but FA seems to change with working memory measures. Working memory is

known to rely on a distributed network of brain areas, and naturally, white matter connectivity is important for working memory performance. As mentioned, mechanisms of activity-induced myelination have been established, as reviewed by Fields (2008) . For instance, findings from the rat optic nerve show that axonal electrical activity promote proliferation of oligodendrocyte progenitor cells (Barres & Raff, 1993). Hence, activity-dependent myelination does occur and may be at play also in cognitive rehabilitation. The present patient trained especially with tasks challenging working memory, and this training may have lead to white matter microstructrual changes.

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