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STRUCTURAL CHANGES IN FUNCTIONALLY ILLITERATE ADULTS AFTER INTENSIVE TRAINING

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Abstract—About 7.5 million adults in Germany cannot read and write properly despite attending school for several years. They are considered to be functional illiterates. Since the ability to read and write is crucial for being employed and socially accepted, we developed a literacy training to overcome these deficits. In this study, we investigate the structural changes induced by the training. A group of 20 functional illiterates and 20 adult normal readers participated in the study. Group differences as well as intervention-related changes in gray (voxel-based morphometry, VBM) and white matter (Tract-Based Spatial Statistics, TBSS, applied to fractional anisotropy, FA, obtained with diffusion tensor imaging, DTI) were assessed in functional illiterates and normal reading controls. VBM analyses revealed decreased gray matter intensities in functional illiterates compared to normal readers before training in several reading-related brain regions such as the superior temporal gyrus, supramarginal gyrus, and angular gyrus. Using TBSS, functional illiterates showed reduced FA values in the genu of the corpus callosum. After training, both the gray matter intensities and FA values increased in functional illiterates and were no longer statistically different from controls' pre-test data. Moreover, the increase was positively correlated with reading and writing skills. The findings suggest that poor literacy skills are associated with several structural abnormalities in reading-related brain areas. In addition, we showed that while literacy skills of functional illiterates improved after training, the structural differences to controls disappeared.

Key words: functional illiteracy, literacy training, evaluation, VBM, TBSS, DTI.

INTRODUCTION

Reading depends on the functional integrity of a distributed network of different brain regions. Three systems have been identified to support the reading process (Grigorenko, 2001): A frontal system (inferior frontal gyrus), a temporo-parietal system (angular and supramarginal gyri, posterior part of the superior temporal gyrus [STG]), and an occipito-temporal system (occipito-temporal area and posterior parts of the middle and inferior temporal gyri). Children strongly rely on the frontal and temporo-parietal circuits during reading, which are involved in phonological processing. This suggests that they read words phonologically by grapheme-to-phoneme conversion (Horwitz et al., 1998; Pugh et al., 2000; Shaywitz et al., 2002; Hoeft et al., 2011). Most adults have developed such fluency and automaticity in word reading that slow and effortful phonologically processes are no longer necessary. Rather, they make greater use of the occipital-temporal circuit which is associated with fast and automatized processing of words. However, this specialization develops late in the course of reading acquisition and is strongly related to reading ability (Booth et al., 2001; Shaywitz et al., 2002, 2007; Ben-Shachar et al., 2011).

The importance of literacy skills becomes particularly evident when people experience difficulties with reading or writing. This applies for example to adults who never attended school and therefore have no experience in reading and writing at all. Those people are often referred to as *illiterates* or *primary illiterates*. The main reasons are physical or other impairments or social circumstances like poverty, child labor, lack of schools, and disapproval of literacy in the country of origin (Ardila et al., 2010).

Primary illiterates must be distinguished from *functional illiterates* who attended school for several years (Egloff et al., 2011; Eme, 2011). Although they received instruction in reading and writing, they left school

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Abbreviations: DRT, Diagnostischer Rechtschreibtest; DTI, diffusion tensor imaging; FA, fractional anisotropy; GM, gray matter; GMC, gray matter concentration; GMV, gray matter volume; ROI, region of interest; STG, superior temporal gyrus; TBSS, Tract-Based Spatial Statistics; TFCE, threshold-free cluster enhancement; VBM, voxel-based morphometry; WLLP, Würzburger Leise-Leseprobe; WM, white matter; WMV, white matter volume.

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with literacy skills that are at least three to four years below the expected level of performance (Greenberg and Lackey, 2006). As a result, they can use written language only to a very limited extent; they are unable to read and understand even short sentences (Eme, 2011). A recent survey concludes that there are about 7.5 million functional illiterates in Germany (14.5% of the adult population, Grotlüschen and Riekmann, 2012). Similar prevalence rates are reported for other industrialized countries, e.g. 9% for France (ANLCI, 2007) or 16% for the United Kingdom (Williams et al., 2003). Functional illiteracy is often associated with specific personal obstacles in childhood concerning school (e.g. truancy, inappropriate instructions, repetition of classes) and family environment (e.g. neglect, drug abuse of parents, abuse, numerous siblings, etc.; Ardila et al., 2010). However, these negative experiences do not apply for all individuals with low literacy skills, and are also not sufficient to let someone become functionally illiterate (Eme, 2011). Accordingly, some researchers propose that functional illiteracy results from cognitive deficits coupled with environmental disadvantages (Greenberg et al., 1997; Greenberg and Ehri, 2002; Eme, 2011). Moreover, a relationship between functional illiteracy and developmental dyslexia is assumed. Greenberg et al. (1997) for example consider functional illiteracy as an adult form of developmental dyslexia not adequately treated in childhood. This assumption is supported by several studies showing similarities between functional illiterates and dyslexics (Greenberg et al., 1997; Greenberg and Ehri, 2002; Grosche and Grünke, 2011; Eme, 2011; Rüsseler et al., 2011). Although only a few studies investigate neuronal reading processes in functional illiterates, there is a bulk of studies dealing with developmental dyslexia. Importantly, children and adults with developmental dyslexia differ in the involvement of the neural circuits in reading-related tasks from normal readers. In contrast to normal readers, dyslexics show increased activity in the inferior frontal cortex and reduced activity in the temporo-parietal and occipito-temporal cortex of the left hemisphere (see overviews by Schlaggar and McCandliss, 2007 and Wandell et al., 2012, as well as the meta-analyses of Richlan et al., 2009, 2011). Due to the functional abnormalities in the anterior and posterior language regions, it has been hypothesized that the reading difficulties might be the consequence of a disconnection between temporo-parietal and frontal regions (Paulesu et al., 1996; Horwitz et al., 1998; Temple, 2002; Peterson and Pennington, 2012). To test this hypothesis, researchers have studied white matter tracts in developmental dyslexia using diffusion tensor imaging (DTI).

DTI is a non-invasive neuroimaging method measuring the diffusion of water molecules in brain tissue (Basser et al., 1994; Le Bihan et al., 2001; Jones and Leemans, 2010). In white matter, water diffuses more easily along the orientation of axonal fibers than in other directions due to anatomical limitations such as the myelin sheath. A commonly used measure of the diffusion is the fractional anisotropy (FA). It has been shown that FA is sensitive for individual differences in white matter properties, and to disease states associated with a loss of white matter (e.g., stroke [Mukherjee et al., 2000] and multiple sclerosis [Werring et al., 1999]).

DTI studies in dyslexic children and adults have shown alterations (relative to non-dyslexic controls) of white matter in left temporo-parietal regions (Klingberg et al., 2000; Beaulieu et al., 2005; Deutsch et al., 2005) and inferior frontal regions (Steinbrink et al., 2008; Carter et al., 2009; Rimrodt et al., 2010). These differences are attributed to structural deficits of the left superior longitudinal fasciculus and the left arcuate fasciculus (see meta-analyses of Vandermosten et al., 2012). Further studies also identified other fiber tracts such as the posterior part of the corpus callosum or the inferior longitudinal fasciculus (Ben-Shachar et al., 2007; Dougherty et al., 2007; Steinbrink et al., 2008; Rollins et al., 2009). These structural changes are supported by functional imaging studies showing a disruption of the functional integration between frontal and temporal brain regions (Shaywitz et al., 2003; van der Mark et al., 2011), which is also present at rest (Schurz et al., 2014).

In addition to white matter tracts, gray matter has been shown to be altered in dyslexia as well. A common method to investigate changes in gray matter volume is voxel-based morphometry (VBM). VBM allows a voxel-by-voxel comparison of local tissue concentrations after the automated separation of gray matter (GM), white matter (WM) and cerebro-spinal fluid (CSF; Richlan et al., 2013). Therefore, VBM is a useful tool to study morphological abnormalities in developmental dyslexia.

Reduced gray matter volume was found in bilateral temporo-parietal and left occipito-temporal regions (e.g., Brown et al., 2001; Brambati et al., 2004; Vinckenbosch et al., 2005; Steinbrink et al., 2008; see also Linkersdörfer et al., 2012 for a meta-analysis and Eckert, 2004 for a review). Additionally, the observed structural deficits overlap with functional underactivation in the fusiform and supramarginal gyri of the left hemisphere (Linkersdörfer et al., 2012).

To date, several functional imaging and electroencephalographic studies have demonstrated that dyslexic children and adults benefit from intervention with regard to their behavioral performance as well as the functional integrity of brain structures implicated in reading. Although different forms of intervention are reported in these studies, similar patterns of normalized activation after training were observed (e.g., Simos et al., 2002; Aylward et al., 2003; Temple et al., 2003; Shaywitz et al., 2004; Richards and Berninger, 2008; Boltzmann and Rüsseler, 2013). Krafnick et al. (2011) demonstrated that these behavioral and functional changes induced by training are also associated with structural changes. Specifically, dyslexic children showed improved reading skills, which were related to increased gray matter volume in different brain regions after eight weeks of a formal, instructional training.

To further investigate effects of literacy on brain mechanisms some research groups have studied primary illiterates. They are either compared to adults who acquired literacy skills in childhood (early literates), or to adults who learned to read in adulthood (late literates). The majority of previous studies included

Brazilian (e.g., Dehaene et al., 2010), Colombian (e.g., Carreiras et al., 2009) or Portuguese (Castro-Caldas et al., 1998; Petersson et al., 2007) participants, who did not attend school due to their socio-cultural background. Since all groups have shared the same cultural background, it is assumed that differences in cognitive abilities and brain organization are directly attributable to their different literacy levels. Altogether, these studies indicate that literacy has effects on various cognitive abilities and the cerebral organization of the brain (see reviews by Castro-Caldas, 2004; Petersson and Reis, 2006; Ardila et al., 2010).

An important study by Carreiras et al. (2009) demonstrated that late literates show more white matter in the splenium of the corpus callosum than illiterate adults. In addition, pronounced interhemispheric connections between the left and right angular gyrus and the left and right occipito-temporal regions were found in late literates. The results suggest that learning to read in adulthood increases the coupling between homologous structures of the left and right hemisphere. This coupling is mediated by white matter fibers running through the splenium of the corpus callosum. A voxel-based morphometry also revealed that former illiterates who learned to read in adulthood had increased gray matter volume compared to a group of illiterate adults in different reading-related brain regions (bilateral angular, dorsal occipital, middle temporal, left supramarginal and superior temporal gyri). These regions correspond in part to regions identified as dysfunctional in developmental dyslexia.

In the present study, we investigate if functional illiterates show similar structural alterations as those found in dyslexic individuals. Using DTI and VBM, we compared gray and white matter volumes of functional illiterates with a group of normally reading adults. We expect that functional illiterates show structural alterations in reading-related brain areas similar to those found in dyslexics. We further investigate if these structural alterations can be modulated by behavioral improvements in reading and writing skills. As Krafnick et al. (2014) have shown, dyslexic children show training-induced structural changes. Moreover, illiterates who learn to read and write in adulthood, show changes in white and gray matter volumes (Carreiras et al., 2009). We assume that similar effects can be observed in functionally illiterate adults who participate in an intensive literacy training.

EXPERIMENTAL PROCEDURES

Participants

Participants were recruited from an adult literacy program offered in Osnabrück, Germany (*AlphaPlus*, Rüsseler et al., 2012). In total, 36 adults received daily training over a period of nine months using a formal literacy instruction approach combined with computer-based exercises. The program was targeted at unemployed functional illiterates. Lessons took place from Monday to Friday between 9 am and 2 pm. During formal literacy instruction the basic rules of mapping graphemes to phonemes were taught in conventional literacy lessons (approx. 2 h daily). The used methods were similar to instructions given to children during regular literacy acquisition. However, specific paper–pencil-based exercises were developed due to the lack of appropriate educational materials for adult basic education. The training began with the reading of syllables; later, short words and sentences were used. One of the main objectives was that participants learn the rules of mapping graphemes to phonemes and internalize the phonological structure of words. Common German letter combinations were trained intensively.

The computer-based exercises were supposed to train different skills relevant for language processing (approx. 2 h daily). This part of the training was supposed to consolidate the achievements made during conventional reading lessons. First, the participants trained their basic visual and auditory perceptual abilities. In eight subtests, participants had to discriminate different features of tones or light flashes (for more information see www.meditech.de). In addition, audio-visual integration processes were trained. Linguistic stimuli like words were visually shown on a computer screen and simultaneously vocalized by a speaker, whose voice was presented via headphones. The participants themselves had to vocalize the presented stimuli into a microphone. It is assumed that the synchronous reading of letters and the vocalizing of words facilitates the audio-visual integration of letters and speech sounds. This idea is based on findings showing that dyslexics have deficits in audio-visual integration (Blau et al., 2009). Moreover, training of audio-visual integration has previously been shown to improve literacy skills in dyslexic children (Kujala et al., 2001; Magnan et al., 2004). Finally, the discrimination of phonemes or consonants with similar sound structures was trained. Via headphones, three-letter pseudowords were presented. All of them had as first letter an *e* and as last letter an *i*. The central character was always a consonant, which varied from trial to trial (e.g. *ebi*, *eki*, *epi*). The participants were asked to type the perceived middle character on a computer keyboard.

Social activities like shopping in the supermarket, cooking, visiting the stadium of the local soccer team or fire department were also part of the program.

/Although the participants had attended school for several years ($M = 8.95 \pm 0.37$ years), they demonstrated poor literacy skills and were considered to be functionally illiterate. At the start of the study, average literacy skills of this group were comparable to students after approximately six month of schooling in the first grade. The members of the control group were recruited from a pool of persons who responded to newspaper advertisements. Experimental group (functional illiterates) and control group (normal readers) were individually matched for age ($T(39) = 0.72$, $p = 0.47$) and gender.

Individuals were included if their reading and writing skills were within a range that can be expected for their age and formal educational status. It was also made sure that they had no former diagnosis of any reading or writing impairment in childhood.

General inclusion criteria for both groups consisted of the following: (1) German as the primary language, (2) age above 18 years, (3) general cognitive ability in the normal range and (4) normal hearing and vision.

The study group comprised 20 functional illiterates participating in a literacy program, 15 males and 5 females with a mean age of 42.70 years (*SE* = 2.09 years; range 25 to 58 years). The control group included 20 non-impaired adults, 15 males and 5 females with a mean age of 44.93 years (*SE* = 3.57 years; range 27–56 years). The control group was scanned only once and was not subjected to a training intervention. This neither would have been warranted as all control participants were fluent readers nor possible as all of them were employed and therefore not able to partake in an extensive training program.

The study was conducted in accordance with the declaration of Helsinki. Furthermore, the study protocol was approved by the ethics committee of the University of Bamberg. All participants gave their written informed consent and were paid for test participation (10 € per hour).

Assessment of reading and writing skills

Reading abilities of functionally illiterate adults was assessed with a standardized German reading test (Würzburger Leise-Leseprobe, WLLP [Küspert and Schneider, 1998]). In this test, 140 written words as well as four pictures next to each word are presented. The participants have to mark the one picture that represents the word on the left side. The test score comprises the number of correctly identified pictures in five minutes. The WLLP is supposed to measure silent reading speed and the ability to decode written words. Writing abilities of functionally illiterate adults was tested with a standardized German writing test for first graders (Diagnostischer Rechtschreibtest, DRT-1 [Müller, 2003]). Here, participants have to write 32 single words from dictation. We used parallel versions of the WLLP and DRT-1 at the beginning as well as at the end of the training in order to assess the effectivity of the training program.

Since there are no specific criteria defining functional illiteracy, the present study refers to different national studies that used a norm-oriented approach. In these studies, participants were classified as functionally illiterate when their performance did not meet at least the performance of an average student of the fourth grade. To assess whether individuals met this criterion, the WLLP was used since it allows a comparison of individual scores with students in first to fourth grade. Using such criteria, the group of functional illiterates can be viewed as a group of severely dyslexic adults.

Due to organizational reasons, formal data on reading and writing ability was acquired only for twelve control participants.

The control group was scanned only once and was not subjected to a training intervention. This neither would have been warranted as all control participants were fluent readers nor possible as all of them were employed and therefore not able to partake in an extensive training program.

Image acquisition

MRI data were recorded using a 3-T SIEMENS Magnetom Allegra head scanner (Siemens, Erlangen, Germany) equipped with a standard quadrature head coil. Participants were positioned on a scanner couch in a slightly dimmed MRI chamber; they wore foam earplugs to reduce scanner noise.

Structural MRI

A T1-weighted structural 3D image of the brain was obtained using the MPRAGE sequence with the following protocol: Slice thickness 1-mm isovoxel, repetition time16 ms, echo time 4.9 ms, field of view 256 × 256 mm, 192 sagittal slices.

Diffusion tensor imaging (DTI)

Diffusion tensor imaging (DTI) data were collected using the following protocol: 2-mm-thick slices, no gap, repetition time 7200 ms, echo time 86 ms, acquisition matrix 128 × 128, field of view 256 × 256 mm, 50 axial slices. Diffusion was measured along 12 non-collinear directions, chosen according to the standard Siemens DTI acquisition scheme using a single b value of 1000 s/mm^2. Three signal averages were acquired per slice and diffusion gradient direction. Each run was preceded by a non-diffusion-weighted volume for purposes of registration for motion correction.

Voxel-based morphometry (VBM)

Structural data were analyzed with FSL-VBM, a voxel-based morphometry style analysis (Ashburner and Friston, 2000; Good et al., 2001) carried out with FSL 5.0.5 tools (Smith et al., 2004). First, structural images were brain-extracted using BET (Smith, 2002). Next, tissue-type segmentation was carried out using FAST (Zhang et al., 2001). The resulting gray-matter partial volume images were then aligned to MNI152 standard space using the affine registration tool FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002), followed by nonlinear registration using FNIRT (Andersson et al., 2007a, b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). The resulting images were averaged to create a study-specific template, to which the native gray matter images were then non-linearly re-registered. The registered partial volume images were then modulated (to correct for local expansion or contraction) by dividing by the Jacobian of the warp field. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm (corresponding to a 7 mm FWHM). Finally, voxel-wise GLM was applied using permutation-based non-parametric testing (5000 permutations). The resulting maps were thresholded at $p < 0.05$ (Family-wise error corrected; FWE) using threshold-free cluster enhancement (TFCE [Smith and Nichols, 2009]) to define clusters of significant changes. Data were visualized in MNI standard space using FSLView.

Tract-Based Spatial Statistics (TBSS)

Voxelwise statistical analysis of the FA data was carried out using TBSS (Tract-Based Spatial Statistics; Smith et al., 2006), part of FSL 5.0.5 (Smith et al., 2004). First, FA images were created by fitting a tensor model to the raw diffusion data using FDT, and then brain-extracted using BET (Smith, 2002). All participants' FA data were then aligned into a common space using the nonlinear registration tool FNIRT (Andersson et al., 2007a,b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centers of all tracts common to the group. Each subject's aligned FA data were then projected onto this skeleton and the resulting data fed into voxel-wise cross-subject statistics. For this purpose we used permutation-based non-parametric testing (5000 permutations). The resulting maps were thresholded at $p < 0.05$ (FWE) using TFCE (Smith and Nichols, 2009) to define clusters of significant changes. Data were visualized in MNI standard space using FSLView.

To investigate interactions between training-dependent effects and psychological scores revealed in this study, bivariate correlations (Pearson's r, $p < 0.05$, two-tailed) were carried out between individual subject measures of gray matter intensity (VBM) or FA (TBSS) and the parameters. Significant clusters identified from the difference between pre- and post-training were thus used as masks to extract mean values from individual data sets. The differences in these values resulting from training and that of psychometric parameters were used to test for correlation.

TBSS provides information on white matter differences at the voxel level, but does not yield information regarding effect sizes. These are important for interpreting the extent of white matter changes. Therefore, the white matter region that showed microstructural differences at the voxel-based level in functional illiterates, i.e. the genu of the corpus callosum, was used as a region of interest (ROI) for further analysis. The ROI was determined using the Johns Hopkins University white matter tractography atlas (Wakana et al., 2004) implemented in FSL, which was applied to the mean white matter skeleton as obtained by TBSS in the current sample. FA was extracted for each individual subject. Two comparisons were performed: (a) between control subjects and functional illiterates before training, (b) between functional illiterates prior and after training. A t-test for independent measures was calculated for a) and a t-test for dependent measures was calculated for (b). Effect sizes (Cohen's d) were calculated using the formulas given by Borenstein (2009) and Dunlap et al. (1996) as implemented in http://www.psychometrica.de/effect_size.html#dep. This approach was similar to that taken by Ameis et al. (2011).

RESULTS

Reading and writing skills

Demographic characteristics and literacy scores for both groups are presented in Table 1.

Reading ability. Before training, the average number of words identified correctly in the WLLP was 135.25 (SE = 1.40) in controls (n = 12) and 39.30 (SE = 5.85) in functional illiterates (n = 20; $T(30) = -12.45$, $p < 0.001$). Although functional illiterates demonstrated substantial gains in reading ability during training (M = 55.20, SE = 7.66; $T(19) = -3.78$, $p < 0.01$), their scores still did not reach the values of control participants after training ($T(30) = -8.00$, $p < 0.001$).

Writing ability. The mean of writing errors (DRT-1) was zero in controls (n = 12) and 16.10 (SE = 2.36) in functional illiterates (n = 20) before training. The difference between both groups was significant ($T(30) = 5.25$, $p < 0.001$). The number of errors significantly decreased in functional illiterates to 10.25 (SE = 1.91) after training ($T(19) = 6.25$, $p < 0.001$). However, their scores still did not reach the values of control participants ($T(30) = 4.14$, $p < 0.001$).

VBM

Gray matter intensity was lower in functional illiterates before training compared to controls in left and right supramarginal gyrus, left and right angular gyrus, left and right precuneus, left and right superior parietal lobule and left parietal operculum (see Fig. 1a and Table 2). There were no areas in which gray matter intensity was higher in illiterates than in controls. After training (comparison illiterates after > illiterates before training), we found an increase of gray matter intensity in functional illiterates as shown in Fig. 1b and Table 3. This increase appeared in the same regions found to be reduced prior to the training.

The contrast controls > illiterates after training revealed no longer areas of abnormal gray matter intensity after training.

In some of the regions identified in the previous analyses we found a significant correlation between

Table 1. Demographic characteristics and literacy skills of functional illiterates and controls

	Functional illiterates (n = 20)		Controls (n = 20)
Sex	15 male		15 male
Age (years)	42.70 (2.09)		44.93 (3.57)
Reading skill (correct words)	Before training	39.30 (5.85)	135.25 (7.66)
	After training	55.20 (7.66)	
Writing skill.	Before training	16.10 (2.36)	0.00 (0.00)
(errors)	After training	10.25 (1.91)	

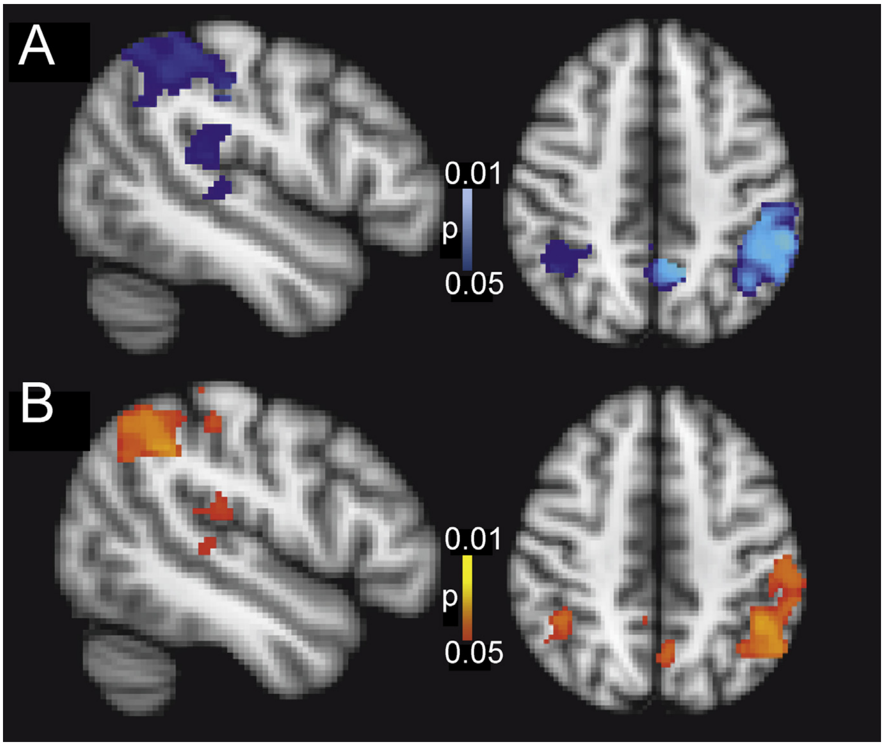

Fig. 1. Voxel-based morphometry: (A) Comparison between controls and functional illiterates before training. The comparison reveals regions of decreased intensity of gray matter in functional illiterates before training compared to controls. (B) Comparison between functional illiterates after training and functional illiterates before training. This comparison shows regions of increased gray matter intensity after training, which were thus interpreted as training-induced. It is noteworthy that areas with decreased gray matter intensity in functional illiterates compared to controls were the same which showed an intervention-related increase. All data are FWE-corrected for multiple comparisons.

gray matter intensity in functional illiterates and their reading ability (WLLP) as well as their writing ability (DRT-1). Specifically, the increase of gray matter intensity after training shows a positive correlation with the increase of the reading score (e.g. left parietal operculum: 0.39; left superior temporal gyrus: 0.62; left superior parietal lobule: 0.42) and a negative correlation with the decrease of the writing score (left superior temporal gyrus: −0.55; left supramarginal gyrus: −0.39; see Table 4).

TBSS and region of interest analysis

Evaluating the DTI data with TBSS we found the left genu of the corpus callosum as the only area with significantly reduced FA in functional illiterates before training compared to control participants (contrast controls > functional illiterates before training, Fig. 2a, Table 5). There were no areas showing a greater FA in functional illiterates before training compared to controls.

After training, we found an increase in FA in this region in functional illiterates compared to the same group before training (Fig. 2b, Table 5). We found no significant difference between controls and functional illiterates after training.

The increase in FA in the left genu of the corpus callosum in functional illiterates correlated positively with the increase in reading ability. The Pearson coefficient (r) was 0.35 ($p < 0.05$, two tailed). The FA showed no significant correlation with changes in writing ability.

To get an estimate of effect size of these white matter changes, we performed a ROI analysis for the genu of the corpus callosum. For the comparison functional illiterates prior to training vs. control participants a significant difference with a moderate to large effect size was

Table 2. Regions with decreased gray matter intensity in functional illiterates before training ($n = 20$) compared to controls ($n = 20$) evaluated with VBM

Brain region	Hemisphere	MNI coordinates			Cluster size	p (FWE)
		X	Y	Z		
Parietal Operculum Cortex	L	−50	−34	18	148	0.03
Superior Temporal Gyrus, posterior division	L	−48	−32	2	30	0.02
Lateral Occipital Cortex, superior division	L	−48	−62	44	273	0.03
Lateral Occipital Cortex, superior division	R	14	−64	54	319	0.02
Superior Parietal Lobule	L	−42	−40	46	255	0.02
Superior Parietal Lobule	R	36	−46	46	270	0.01
Precuneus Cortex	L	−4	−56	46	283	0.02
Precuneus Cortex	R	6	−58	48	65	0.02
Angular Gyrus	L	−48	−54	40	231	0.01
Angular Gyrus	R	46	−52	50	72	0.02
Supramarginal Gyrus, anterior division	L	−58	−38	46	329	0.01
Supramarginal Gyrus, anterior division	R	50	−40	46	32	0.02
Supramarginal Gyrus, posterior division	L	−50	−48	48	278	0.01
Supramarginal Gyrus, posterior division	L	40	−42	46	64	0.01

Table 3. Regions with increased gray matter intensity in functional illiterates after training ($n = 20$) compared to before training evaluated with VBM

Brain region	Hemisphere	MNI coordinates			Cluster size	*p* (FWE)
		X	*Y*	*Z*		
Parietal Operculum Cortex	L	−46	−28	20	125	0.02
Superior Temporal Gyrus, posterior division	L	−50	−34	6	34	0.02
Lateral Occipital Cortex, superior division	L	−50	−60	46	269	0.02
Lateral Occipital Cortex, superior division	R	16	−60	56	224	0.03
Superior Parietal Lobule	L	−48	−46	46	260	0.02
Superior Parietal Lobule	R	40	−50	50	221	0.02
Precuneus Cortex	L	−2	−62	48	205	0.01
Precuneus Cortex	R	8	−50	50	70	0.02
Angular Gyrus	L	−46	−52	40	220	0.01
Angular Gyrus	R	44	−50	52	77	0.02
Supramarginal Gyrus, anterior division	L	−56	−30	48	340	0.02
Supramarginal Gyrus, anterior division	R	48	−38	50	28	0.02
Supramarginal Gyrus, posterior division	L	−48	−50	44	254	0.01
Supramarginal Gyrus, posterior division	R	42	−44	48	81	0.02

Table 4. Regions with increased gray matter intensity in functional illiterates after training ($n = 20$) compared to before training evaluated with VBM in which we found significant correlation to WLLP and DRT1. The table shows the Pearson coefficient (r). The significant parameters are marked as follows: $^{*}p < 0.05$; $^{**}p < 0.005$; $^{***}p < 0.0005$; two tailed

Brain region	Hemisphere	Reading (WLLP)	Writing (DRT-1)
Parietal Operculum Cortex	L	0.39*	−0.28
Superior Temporal Gyrus, posterior division	L	0.62***	−0.55***
Lateral Occipital Cortex, superior division	L	0.35*	−0.34*
Lateral Occipital Cortex, superior division	R	0.34*	−0.21
Superior Parietal Lobule	L	0.42**	−0.27
Superior Parietal Lobule	R	0.37*	−0.25
Angular Gyrus	R	0.33*	−0.26
Supramarginal Gyrus, anterior division	L	0.32*	−0.13
Supramarginal Gyrus, anterior division	R	0.38*	−0.16
Supramarginal Gyrus, posterior division	L	0.39*	−0.39*

obtained for FA ($t = 2.78$, df = 38, Cohen's $d = 0.87$). For the comparison of the functional illiterates prior and after the training, a paired t-test revealed again a significant effect ($t = 2.18$, df = 19, Cohen's $d = 0.689$).

DISCUSSION

The present study examined structural changes in functionally illiterate adults after literacy training using DTI and TBSS. For the first time, gray and white matter volumes were investigated in a group of functional illiterates. Our main finding was that functional illiterates showed reduced gray matter volume (GMV) in different reading-related brain areas (e.g., lateral occipital cortex, superior temporal gyrus, angular gyrus, supramarginal gyrus, and precuneus) compared to normal readers. Importantly, there was an increase of gray matter intensity in functional illiterates due to training as revealed by the before/after training comparison in this group. Moreover, there were no longer any differences in GMV of impaired and normal readers after nine months of literacy training. This enhancement likely has been induced by participating in the literacy training, as behavioral improvements in reading and writing were positively related to these structural changes.

Reading processes require the cooperation of three distinct and distributed brain systems: A frontal, a temporo-parietal, and an occipito-temporal system. The temporo-parietal system is involved in the phonological analyses of words, and is important during reading acquisition when children learn to decode words by grapheme-phoneme-conversion. Accordingly, it has been shown that activations of the superior temporal gyrus (Turkeltaub et al., 2003), the angular gyrus and the supramarginal gyrus (Booth et al., 2001) increase during reading acquisition. In adult normal readers, temporo-parietal regions are engaged in reading unfamiliar words like pseudo-words which require phonological decoding (Price et al., 1996; Simos et al., 2000; Xu et al., 2001). The significance of these brain regions for reading processes also becomes evident when dyslexic children and adults are considered. They show reduced functional activity during phonological tasks (e.g., Rumsey et al., 1997; Shaywitz et al., 1998, 2002) as well as reduced gray matter volume (Linkersdörfer et al., 2012; Richlan et al., 2013) in temporo-parietal regions.

The findings of the present study demonstrate that adults, who are considered to be functionally illiterate show similar reductions in gray matter volume in temporo-parietal brain regions as dyslexic children and adults. Due to their low reading and writing scores it is

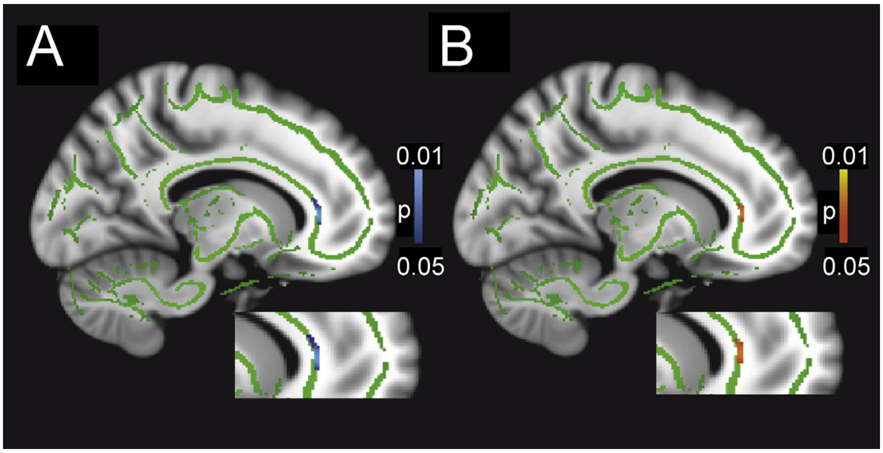

Fig. 2. TBSS analysis of DTI images. (A) The comparison of controls > functional illiterates before training revealed decreased FA in the latter. (B) The comparison of functional illiterates after training > functional illiterates before training revealed an increase in FA after training in the same area. The background image is the standard FMRIB58_FA_1 mm template in FSL. The green voxels show the mean FA skeleton representing the centers of all of the tracts common to the group. Blue/Red-Yellow voxels represent regions described above. All data are FWE-corrected for multiple comparisons. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

likely that their reading strategies resemble those of children using grapheme-phoneme-conversion to decode words phonologically. But unlike children, functional illiterates were not able to develop functional phonological skills, which might impact the structure and function of those brain regions involved in phonological processing. In line with this assumption, we found an increase in gray matter volume in the superior temporal gyrus, angular gyrus and supramarginal gyrus after participants attended a literacy training program of 9-month duration. Although the training program was a multi-method approach, the focus was on the training of phonological skills. Similar to children, participants learned to decode words by grapheme-phoneme-conversion. As a result, the phonological skills of the participants improved during training, which is reflected in higher reading and writing scores. The improvements in behavioral measures in turn are related to the structural changes.

An important issue is related to the question whether the observed reduction of GMV in functional illiterates before training is the cause for their difficulties or a consequence of the persistent problems with reading and writing. Although we cannot answer this question directly, a recent study investigated this issue in dyslexic children. Krafnick et al. (2014) compared dyslexic children with two groups of non-dyslexic children, one group at the same age-level and one group at the same reading level as the dyslexic children. As a result, the dyslexic group showed reduced GMV in several reading-related brain areas when compared to age-matched controls. However, when compared to reading-matched controls most of these regions did not emerge as different. The authors conclude that differences between dyslexic and non-dyslexic children are in part a result of the impaired reading abilities of dyslexic children. Because they read qualitatively different compared to children of the same age, the gray matter volume in relevant brain regions did not develop in the same way as they did in typically developed children. This assumption is supported by the study of Krafnick et al. (2011) demonstrating increases in GMV in dyslexic children following training-related behavioral improvements in reading and writing abilities. Although Krafnick and colleagues were the first who reported changes of gray matter in dyslexic children after training, the study has two important shortcomings: The small sample size of the dyslexic group, which consisted only of 11 participants, and the missing control group receiving no or an alternative training. However, evidence for GMV increases in adults has been provided for other areas of training as well. For example, adults who learn to juggle (e.g., Draganski et al., 2004; Driemeyer et al., 2008) or to read mirror writing (Ilg et al., 2008), as well as medical students preparing for their final exams (Draganski et al., 2006), show increases in gray matter volume of brain areas known to support the trained functions.

Studies with primary illiterates, i.e. adults who never attended school, suggest that learning to read has an influence on a variety of cognitive functions (see Ardila et al., 2010 for a review), as well as on the functional and structural organization of the brain (Carreiras et al.,

Table 5. Regions showing a significant change of FA evaluated with TBSS and using DTI images. A < C: Regions showing a significant decrease in FA in functional illiterates before training (n = 20) compared to controls (n = 20). B > A: Regions showing a significant increase in FA in functional illiterates after training (n = 20) in contrast to before training

Brain region	Hemisphere	MNI coordinates			Cluster size	p (FWE)
		X	Y	Z		
A < C						
Genu of corpus callosum	L	−10	32	6	201	0.03
B > A						
Genu of corpus callosum	L	−14	35	5	144	0.02

2009; Castro-Caldas et al., 1998, 1999; Dehaene et al., 2010). According to Carreiras et al. (2009), adults who learned to read in adulthood (late literates) showed more gray matter in several temporo-parietal regions than illiterate adults. This can be seen as evidence for an experience-dependent increase in gray matter volume. In line with our study, the differences mainly occurred in regions relevant for phonological processing such as the superior temporal, the angular and the supramarginal gyri.

Also in accordance with our findings, no changes were found for the fusiform gyrus. The fusiform gyrus is part of the occipito-temporal system and is associated with the recognition of familiar orthographical word forms (e.g., Dehaene et al., 2002; Fiebach et al., 2002; Binder et al., 2003). Several functional imaging studies examining the development of this region during reading acquisition reveal an increase in activity in the left hemisphere with reading experience (Simos et al., 2001; Schlaggar et al., 2002; Shaywitz et al., 2002) and a decrease in activity in the right hemisphere (Simos et al., 2001; Turkeltaub et al., 2003, 2005). Skilled readers rely on this region to recognize well-known words for which they have developed a visual expertise (for a review see Schlaggar and McCandliss, 2007). The gray matter volume of the fusiform gyrus is modulated by reading skills of children (Simon et al., 2013) and adults (Frye et al., 2010). Furthermore, Dehaene et al. (2010) demonstrated functional differences between illiterates and literates in this area. Again, fusiform activity was positively correlated with reading ability (Dehaene et al., 2010). However, we found no differences between good and poor readers in the fusiform region, similar to Carreiras et al. (2009). It is likely that the link between functional activity and structural modulation is more complex than it appears (Simon et al., 2013).

In the present study, the group of functional illiterates also did not show any structural differences in inferior frontal regions before or after training. Those regions are usually engaged when words have to be read by grapheme-phoneme-conversion due to unknown or infrequent phonological representation (Pugh et al., 1996; Shaywitz et al., 1998; Poldrack et al., 1999). Accordingly, children consistently rely on frontal brain regions; specifically the inferior frontal gyrus (Simos et al., 2001; Schlaggar et al., 2002).

The role of the inferior frontal cortex in dyslexia is somewhat controversial. While some researchers report underactivations of the inferior frontal gyrus in dyslexic readers (Shaywitz et al., 2002), others found no differences (Rumsey et al., 1997; Paulesu et al., 2001) or even overactivations in dyslexic readers (Shaywitz et al., 1998; Brunswick et al., 1999; Temple et al., 2001). However, Shaywitz et al. (2002) revealed a positive correlation between chronological age and the activation of the inferior frontal cortex. They conclude that frontal regions are involved with increasing age in phonological processes to compensate for the dysfunction in posterior regions.

There is also some evidence for structural abnormalities in inferior frontal regions associated with dyslexia. For example, Brown et al. (2001) found reduced gray matter in the left inferior frontal gyrus in dyslexic readers. In support of this finding, there seems to be a correlation between the gray matter structure in this region and phonological skills (e.g., Vinckenbosch et al., 2005). On the other hand, most studies found no differences in gray matter in inferior frontal regions. Accordingly, structural abnormalities of GMV in this area might not be a causal factor in the neurobiological origin of dyslexia (see Linkersdörfer et al., 2012).

DTI changes

Another important finding of the present study is that functional illiterates showed reduced fractional anisotropy in the left genu of the corpus callosum compared to controls which suggests impaired quality of white matter in this region. The corpus callosum harbors myelinated fibers serving information transfer between the left and the right hemisphere. Importantly, we found no group difference after nine months due to normalized FA values in functional illiterates.

A similar result is reported by Keller and Just (2009) who compared 8- to 10-year-old good and poor readers. A phonological training with a duration of 100 h resulted in white matter changes in an anterior region, where FA previously had been reduced in poor readers.

Several MRI studies demonstrated abnormalities in the corpus callosum of dyslexic children and adults relating to the splenium (Duara et al., 1991; Rumsey et al., 1996, 1999), the isthmus (Rumsey et al., 1996, 1999) and the genu (Hynd et al., 1995).

The posterior midbody of the corpus callosum for example is smaller in dyslexic children than in normal readers (von Plessen et al., 2002). This region develops late in childhood when children learn to read and is supposed to connect the left and right primary and secondary auditory cortices. These results are consistent with morphological findings observed in functionally illiterate adults. For example, the splenium of the corpus callosum has been shown to be thinner in illiterates than in normal adult readers (Castro-Caldas et al., 1999). Moreover, Petersson et al. (2007) found lower intensity of white matter in the posterior third of the corpus callosum of illiterate adults. This difference in the corpus callosum was part of a larger cluster that extended bilaterally in inferior parietal and temporo-parietal regions. According to Castro-Caldas and Reis (2000), reading promotes the exchange of information between both hemispheres. As a consequence, an increase in white matter tissue is caused in specific regions of the corpus callosum, which connect reading-related areas of the left and right hemisphere. Accordingly, illiterates who lack reading experience demonstrate morphological reductions in relevant parts of the corpus callosum. This notion is supported by Carreiras et al. (2009), who found increased white matter in the splenium of the corpus callosum in late literates compared to illiterate adults.

In another study, 16 dyslexic children were compared with 16 age-matched controls (Hynd et al., 1995). This time, significant differences were found for the genu of the corpus callosum, which was smaller in dyslexics.

The genu contains fibers, which connect frontal brain regions. The morphological differences were interpreted as a result of impaired functions localized in these brain regions, e.g. processing of written language. According to Hynd et al. (1995) there is a direct correlation between reading performance and the size of the genu. These white matter abnormalities are also associated with reduced gray matter volume in frontal regions.

One problem with many reports in the literature is that the reported morphological changes of the corpus callosum of dyslexic individuals could also result from differences in handedness and/or gender distribution in dyslexic and control groups. Careful matching of these factors in the present study makes these factors an unlikely explanation of the present findings.

The question arises as to how our two findings, VBM-changes of gray matter intensity on the one hand and changes of FA in the corpus callosum on the other hand, could be related. We believe that they are both results of a more intense usage of the reading network in functional illiterates after the training intervention. The increased need for interhemispheric transfer of information likely underlies the callosal changes, whereas the gray matter changes in superior temporal, lateral occipital regions, the angular and supramarginal gyri appear to be related to increased usage of the reading system. An interesting question is whether a study with more participants would be able to also demonstrate white matter changes regarding the tracts connecting the gray matter areas pinpointed by the present experiment.

Although evidence for the structural plasticity of the adult brain has been provided for different domains and for different samples, the meaning of macroscopic changes of gray and white matter in terms of microscopic changes (e.g., synaptic density, sprouting of dendrites) is still not very well understood. It seems plausible that a behavioral improvement is associated with changes in gray or white matter. In Alzheimer's and other degenerative diseases, it is understandable that the death of neurons leads to a reduction in gray matter, which is detected with VBM. But what about increases in gray matter intensity or FA (Mechelli et al., 2005)? It is not clear whether an increase in gray matter induced by experience-related learning is caused by changes in the density of synapses or spines, the size of neurons or glia cells, or the genesis of new cells. This is an important question in the context of VBM studies, but cannot definitely be answered with common MRI methods. However, increased density of gray matter after only one week of training (Driemeyer et al., 2008) tends to favor changes in the synapse and spine density or increase in cell bodies instead of the genesis of new neurons or glia cells. Long-lasting changes on the other hand, as the changes in GMV of the hippocampus (Draganski et al., 2006), might rather reflect slow processes like the genesis of new neurons or glia cells (Mechelli et al., 2005).

To determine the underlying changes, structural methods such as VBM or DTI should be directly combined with histological examinations. In such an approach, Suzuki et al. (2013) investigated the relationship between changes in gray matter (using VBM) and histological damage (counting the number of neurons and microglia) in an animal study with rats. After a cardiopulmonary resuscitation, rats showed reduced gray matter concentration (GMC) as well as neuronal loss in a hippocampal region. Moreover, GMC was positively correlated with the number of neurons and negatively correlated with the number of microglia. The authors concluded that changes in the gray matter concentration represent a marker for the underlying neuronal damage (Suzuki et al., 2013). However, studies in other research domains (e.g., developmental dyslexia, functional illiteracy) are needed to answer the question, which microscopic changes cause alterations in gray or white matter.

Technical considerations and limitations

Every neuroimaging study must make choices with regard to analysis strategy. In this case, we adopted the increasingly popular TBSS-framework to analyze white matter changes and preferred it over previously used VBM-based analysis of DTI (e.g., Jones et al., 2005). We are aware that TBSS itself comes with a number of potential problems including (a) the fact that the shape of the skeleton and hence the statistical results may be rotationally variant (Edden and Jones, 2011), (b) problems with registration misalignment (Zalesky, 2011), (c) dependence of the results on the registration target (Keihaninejad et al., 2012), and (d) partial volume or voxel averaging artifacts resulting from filtering with isotropic smoothing kernels (van Hecke et al., 2010). Suggestions have been made to improve TBSS (e.g., Bach et al., 2014) but this method in our view presently still is an adequate and probably optimal choice for the analysis of white matter changes. Likewise, with regard to VBM analysis of gray matter changes, alternative methods such as cortical thickness analysis (Fischl and Dale, 2000; MacDonald et al., 2000) have been proposed. In the current investigation we preferred to use VBM because of its proven reliability. Also, a group size of 20 is on the lower limit of an acceptable sample size for morphometric studies. Because of the considerable demands on logistics and time that was entailed in the present study, a larger sample size was not possible at present. Thus, a replication of the current study in a larger group is highly desirable.

CONCLUSION

This study investigated training-related changes in gray and white matter in an adult sample of functional illiterates. As hypothesized, adults with severe reading deficits showed similar reductions in gray matter volume as children and adults with dyslexia. Moreover, participating in an intensive literacy program over a period of nine months led to an increase in gray matter volume as previously reported for children with dyslexia (Krafnick et al., 2014). Similar changes were found in white matter of the genu of the corpus callosum, which was reduced before training.

We conclude that intensive literacy training leads to changes in gray and white matter volumes of functional illiterates.

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Authors contribution: JR and MB designed the study. MB and BM acquired the data. BM and AS analyzed the data. MB, JR, TFM and BM wrote the paper.

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