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# White matter hyperintensities increases with traumatic brain injury severity: associations to neuropsychological performance and fatigue

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## ABSTRACT

**Objective:** To examine the prevalence of white matter hyperintensities (WMHs) in patients with traumatic brain injury (TBI) as compared to healthy controls, and to investigate whether there is an association between WMH lesion burden and performance on neuropsychological tests in patients with TBI.

**Methods:** A total of 59 patients with TBI and 27 age- and gender-matched healthy controls underwent thorough neuropsychological testing and magnetic resonance imaging. The quantification of WMH lesions was performed using the fully automated Lesion Segmentation Tool.

**Results:** WMH lesions were more common in patients with TBI than in healthy controls ( $p = .032$ ), and increased with higher TBI severity ( $p = .025$ ). Linear regressions showed that WMH lesions in patients with TBI were not related to performance on any neuropsychological tests ( $p > .05$  for all). However, a negative relationship between number of WMH lesions in patients with TBI and self-assessed fatigue was found ( $r = -0.33$ ,  $p = .026$ ).

**Conclusion:** WMH lesions are more common in patients with TBI than in healthy controls, and WMH lesions burden increases with TBI severity. These lesions could not explain decreased cognitive functioning in patients with TBI but did relate to decreased self-assessment of fatigue after TBI.

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## Introduction

White matter hyperintensities (WMH) are lesions in white matter, detectable with fluid-attenuated inversion recovery (FLAIR) imaging during magnetic resonance imaging (MRI) examinations. WMHs are common in normal aging(1), and increased WMH lesion burden is often seen in patients affected by various disorders to the brain, such as stroke(2), diabetes mellitus(3), schizophrenia(4), multiple sclerosis(5), dementia(6), and traumatic brain injury (TBI) (7–10). In TBI, the mechanical forces applied to the brain may cause microbleeds, shearing and/or degraded axon integrity in cerebral white matter. These injuries appear as white hyperintense areas in the FLAIR image. Thus, WMHs are more common in patients with TBI than in the general population (9,10). Studies have also indicated that WMHs lesion burden after TBI is related to both injury severity (8,9,11), and outcome (8,11–13).

WMHs could also be a factor explaining the reduced cognitive function after a TBI. However, only a few studies have examined the relationship between WMHs and cognition or self-experienced symptoms, with conflicting results (14–16). One explanation for these diverse results may be unreliable quantification of WMH lesions. Although visual inspection using scales such as Fazekas (17) and Scheltens (18) show

satisfying intra- and interobserver reliability, automated WMH lesion tools are more precise, more reliable and rapid when quantifying WMH lesions(19).

The first objective of this study was to compare patients with TBI to age- and gender-matched healthy controls regarding frequency and volume of WMH lesions, as determined by the fully automated Lesion Segmentation Tool (LST; [www.statistical-modeling.de/lst.html](http://www.statistical-modeling.de/lst.html)). The second objective was to determine the relation between the frequency and volume of WMHs and TBI severity. The final objective was to investigate the relationship among TBI-related WMHs, neuropsychological performance, and fatigue. We included neuropsychological measures of several different cognitive functions. The first step was to examine if there were differences between healthy controls and patients with TBI in these measures. In a second step, we probed whether WMHs moderated these differences.

## Materials and methods

### Participants

All patients with TBI were recruited from a previous clinical trial(20), where a detailed description of the recruitment process and inclusion and exclusion criteria have been extensively described. Inclusion criteria were TBI > 1 year previously, age

18 to 65 years, and moderate disability or better recovery according to the Extended Glasgow Outcome Scale(21). Further, all patients suffered from self-experienced fatigue, defined as a Fatigue Severity Scale (22) score >36. In short, exclusion criteria were other psychiatric or neurologic disorders, substance abuse, liver-, heart-, kidney- or neoplastic disease, and history of epileptic seizures. Reported TBI severity was based on length of loss of consciousness at time of injury according to the VA/DOD clinical practice guideline (23). This data was gathered either by patient self-report or, when available, confirmed in medical records. A total of 60 patients underwent MRI examination, but one ended the examination before any FLAIR images were acquired and was therefore not included in the analysis. Of these 59 patients, 55 returned for the follow up MRI scan. In all analyses, except for the test-retest reliability analysis, the first scan of all 59 patients was used.

Healthy controls were recruited among family and friends of patients with an interest to participate in the study. The recruitment process of these has previously been extensively described(24). In short, the healthy participants had the same inclusion and exclusion criteria as patients, with the addition of never having suffered a concussion or more severe head injury. A total of 30 healthy controls went through all examinations. Three of these were excluded due to incidental findings during the MRI examination, or scoring above cutoffs for clinical conditions on self-assessment scales. Thus, a total of 27 healthy controls were included in the analysis.

Demographical characteristics of the patients with TBI and the healthy controls can be seen in Table 1. There were no differences between groups in age or distribution in gender. However, there were significant differences in education ( $p = .03$ ) and employment status ( $p < .001$ ), where healthy controls had higher education, and were working/studying at a higher degree.

### Neuropsychological measures

All participants went through extensive neuropsychological testing with the following tests in the following order: Rey Auditory Verbal Learning Test (25) (measuring mainly

episodic learning); Coding (processing speed) from Wechsler Adult Intelligence Scale, 4th edition (WAIS-IV (26)); Digit Span (working memory) from Wechsler Memory Scale, 3rd edition (WMS-III (27)); Trail Making Test (attention and executive functions) from Delis-Kaplan Executive Functions System (D-KEFS (28)); Rey Auditory Verbal Learning Test Delayed Recall (episodic memory recall); Paced Auditory Serial Addition Test (29) (attention and processing speed); Symbol Search (processing speed) from WAIS-IV; Block Span (working memory) from WMS-III; Color-Word Interference Test (executive functions) from D-KEFS; and Verbal Fluency (executive functions) from D-KEFS. All participants also completed two self-assessment scales of fatigue in everyday life, the Fatigue Severity Scale (FSS (22)) and the Mental Fatigue Scale (MFS (30)).

### Procedure

This study was approved by the regional ethics board in Umeå University, Sweden and was performed following the principles of the Declaration of Helsinki. At start of the study, all participants read and signed informed consent before beginning examinations. All patients with TBI performed the assessments on two occasions. The neuropsychological tests and self-assessments of fatigue were performed on 1 day, and the MRI imaging procedure, including fMRI with task(31), were performed 1 week later. Healthy controls underwent all examinations in 1 day, starting with the MRI imaging procedure, followed by a 30-min break and continuing with neuropsychological tests and self-assessment scales. Patients with TBI also underwent an identical MRI imaging procedure 28 days later, after completing a clinical trial (20) that should not affect the structure of the brain. This latter scan was used in the reliability analysis only.

### Magnetic resonance imaging procedure

A 3T Discovery MR 750 General Electric scanner (General Electric Company, Chicago, IL, USA) were used on all scanning occasions. The fMRI session with the fMRI task was performed first, followed by anatomical imaging acquisition. T1-weighted images were collected using a 3D fast spoiled gradient-echo sequence with 176 slices, and a slice thickness of 1 mm. Repetition time 8.2 ms, Echo time = 3.2 ms, flip angle = 12° and field of view = 25 × 25 cm. Fluid-attenuated inversion recovery (FLAIR) images were acquired using a 2D T2 FLAIR sequence in 48 slices with 3 mm thickness; Repetition Time: 8000 ms, Echo Time: 120 ms, field of view: 24 × 24 cm.

### Statistical analyses

WMH lesions were segmented in SPM12 with the Lesion Segmentation Tool (LST) toolbox version 2.0.15 ([www.statistical-modeling.de/lst.html](http://www.statistical-modeling.de/lst.html)) using the lesion growth algorithm (32). This algorithm first segments T1 images into white matter, gray matter and cerebrospinal fluid, and subsequently combines this with coregistered FLAIR intensities to obtain hyperintense lesions in white matter. The prechosen initial threshold for the created lesions map was set to .3, as default

Table 1. Demographics.

	Patients with TBI (n = 59)		Healthy Controls (n = 27)		Group difference
	M	SD	M	SD	p-value
Age	42.20	13.33	38.15	12.29	.184
Years since injury	8.64	7.27			
Gender (m/f)	32/27		14/13		.837
TBI Severity					
- Mild	40				
- Moderate	11				
- Severe	8				
Education					.030
- Primary School	7		0		
- Vocational School	8		2		
- Upper secondary school	27		9		
- University	17		16		
Employment status					<.001
- Full time work/studies	18		24		
- Part time work/studies	14		3		
- Sick leave/retired	27		0		

and recommended by the developers(33). The result from this analysis is a lesion probability map. Due to skewness in the distribution of both WMH lesion volume and number of WMH lesions, all analyses with these as dependent variables used non-parametric tests, Mann–Whitney U for two groups and Kruskal–Wallis for three groups or more. Spearman’s tests were used for correlations to test for test-retest-reliability of the scanning and analysis procedure between two MRI scans in patients. The correlation between the two scanning occasions in patients with TBI was very strong both regarding number of WMH lesions ( $r = 0.94$ ,  $p < .001$ ) and WMH lesion volume ( $r = 0.96$ ,  $p < .001$ ), indicating high test-retest reliability. To investigate relationships between TBI-related WMHs and neuropsychological measures, linear regression analysis were performed. In the first, unadjusted analysis, the neuropsychological measure of interest was used as the dependent variable and group (TBI or healthy control) was used as predictor. In the next step, WMH lesion volume or number of WMH lesions were included as a covariate. The last, fully adjusted model, included group (TBI or control), age, education level, and WMH lesion volume or number of WMH lesions. Linear regressions were also performed in the TBI group only, with WMH lesions as explanatory variable, with age and education as covariate, and neuropsychological measures and self-assessments of fatigue as dependents.

## Results

At least one WMH lesion was present in 59.3% of healthy controls and 81.4% of patients with TBI. Patients with TBI had a higher degree of number of WMH lesions ( $p = .032$ ) and total WMH lesion volume ( $p = .025$ ; Figure 1). When healthy controls were compared with the different TBI severity subgroups it was found that they differed from both the moderate ( $p = .049$  for number of WMH lesions and  $p = .032$  for lesion volume) and

severe ( $p = .009$  for number of WMH lesions and  $p = .005$  for lesion volume) TBI groups, but not from the mild TBI group.

Comparison of the three groups of patients with TBI showed a significant group difference for both number of WMH lesions ( $p = .043$ ) and lesion volume ( $p = .011$ ). Follow-up Mann–Whitney U tests revealed that patients with mild TBI had a lower number of WMH lesions ( $p = .017$ ) and lesion volume ( $p = .006$ ) than patients with severe TBI. There was also a trend toward patients with mild TBI having lower degree of WMH lesion volume than patients with moderate TBI ( $p = .079$ ). No significant differences between patients with moderate versus severe TBI were observed when it comes to WMH lesions (all  $p$ ’s  $> .10$ ), likely due to the low number of observations (cf., Figure 1).

## Relations among white matter hyperintensities and neuropsychological data

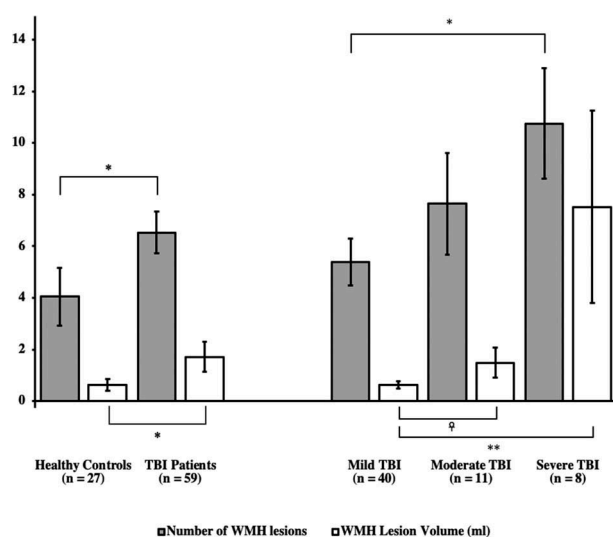
Linear regression analyses (Table 2) revealed significant differences between healthy controls and patients with TBI on all measures of fatigue and neuropsychological tests (all  $p$ ’s  $< 0.05$ ), except for PASAT, Block span and the Verbal Fluency tests. Adjusting for WMH lesion volume or number of WMH lesions, education and age did not change the associations regarding self-assessment of fatigue. However, for most neuropsychological test, the differences between healthy controls and patients with TBI were no longer significant. Only the tests Coding, Symbol Search and Color-Word Interference Test: Inhibition/Switching showed significant differences between groups in the fully adjusted model. In the fully adjusted models, WMH lesion volume or number of WMH lesions was not related to performance in any neuropsychological test. In contrast, number of lesions was in the fully adjusted model negatively related to self-assessment of fatigue on the MFS ( $p = .010$ ), indicating lower self-assessment of fatigue with higher lesion load.

To further investigate the contribution of TBI-related WMH lesions to neuropsychological measures, linear regressions were performed within the TBI group only. In the fully adjusted models with lesion volume, age, and education, WMH lesions were not significantly related to any outcome. However, number of lesions were significantly negatively related to the MFS in the fully adjusted model ( $r = -0.35$ ,  $p = .024$ ), indicating less fatigue with increased lesion load.

## Discussion

In the present study, we found a higher degree of both number and volume of WMH lesions in patients with TBI than in age- and gender-matched healthy controls. Further, there was a steady increase in both number of WMH lesions and volume with increasing TBI severity. Thus, patients with mild TBI showed significantly lower degree of WMH lesions than patients with moderate and severe traumatic brain injury. In summary, these data confirm results from previous studies (8,9,11) that WMH lesion load is related to injury severity. For the first time, this has been shown using the automated lesion segmentation tool LST.

The moderate and severe TBI groups differed from healthy controls in both WMH lesion variables, but the mild TBI group did not. This is in support of previous evidence that patients with



**Figure 1.** Mean number of white matter hyperintensity (WMH) lesions and total WMH lesion volume in healthy controls and patients with traumatic brain injury (TBI). The bars on the left represent all healthy controls and all patients with TBI, while the bars to the right represent patients with TBI divided after TBI severity (Mild, Moderate, Severe). Error bars indicate standard error of mean. Stars indicate significant differences: \* $p < .05$ ; \*\* $p < .01$ ; † $p = .079$ .

**Table 2.** Results from linear regressions comparing healthy controls and patients with TBI.

	Unadjusted	Lesion Volume	Lesion Volume, Age, Education	Nr of Lesions	Nr of Lesions, Age, Education
Fatigue Severity Scale	23.94***	24.13***	23.95***	24.30***	24.00***
Mental Fatigue Scale	14.4***	14.50***	14.27***	14.72***	14.37***^
Rey Auditory Verbal Learning Test: learning	-5.89*	-5.17*^	-2.78†	-5.43*	-3.07''††
Rey Auditory Verbal Learning Test: delayed recall	-1.85*	-1.58*^	-0.98†	-1.65*	-1.07''†
Coding	-23.62***	-23.13***	-17.58***''†††	-22.55***	-17.73***''†††
Digit span total	-2.00*	-1.87*	-1.17†	-1.80*	-1.19†
Trail-Making Test: number sequencing	9.22*	8.41*	4.86†	8.34*	5.10††
Trail-Making Test: number-letter switching	44.66**	42.34*	28.84†	40.91*	29.51†
Paced Auditory Serial Addition Test	-3.07	2.27^	-0.48††	-2.65	-0.83''††
Symbol search	-12.74***	-12.19***^	-10.43***''†	-11.99***^	-10.53***''†
Block span total	-0.60	-0.56	0.12''†	-0.46	0.10''†
Color-Word Interference Test: inhibition	13.66*	13.68*	9.88	13.56*	10.11'
Color-Word Interference Test: inhibition/switching	28.16***	26.94***	24.21***'	26.77***	24.57***'
Verbal Fluency: word fluency	-3.76	-3.46	-1.66	-4.30	-2.05†
Verbal Fluency: category fluency	-5.38	-4.88	-3.12†	-5.80*	-3.44†
Verbal Fluency: category switching	-1.58*	-1.56	-0.99†	-1.60*	-1.04†

Note: Values indicate the unstandardized coefficient (difference) between healthy controls and patients with TBI. Symbols denote significant contribution of that variable to the regression. \*Healthy Controls vs TBI; ^WMH lesion; ^Age; †Education. Number of symbols indicate *p*-value: 1 symbol: *p* < .05; 2 symbols: *p* < .01; 3 symbols: *p* < .001.

mild TBI do not always display structural changes after MRI(34), in this case, white matter lesions as indicated by WMH on the FLAIR sequence. Nevertheless, the association between more severe TBIs and WMH is of clinical interest since both TBIs (35–38) and WMHs (6,39) have been strongly associated with the risk of dementia, and in particular vascular dementia (37,38). One hypothesis to explain the associations between TBI and dementia is that a TBI reduces the cognitive reserve(40). A purpose of the present study was therefore to evaluate if the association between TBI and the different measures of cognitive function was influenced by the degree of WMH. However, the results showed that the lower cognitive function in individuals with a previous TBI was largely unaffected by WMH lesion burden. Furthermore, no neuropsychological test result was related to WMH lesions in the age and education-adjusted models in the TBI-group. The results from these analyses indicate that TBI-related WMH lesions are not connected to performance on several neuropsychological tests, and therefore it is still unclear whether WMH lesions after TBI is a contributing factor to the increased risk of dementia.

Previous studies have indicated associations between different measures of cognitive performance and WMH lesions in patients with TBI, such as episodic memory(14), working memory(15), and mental speed, attention and executive functions(16), although results between studies have been contradictory. Our study included neuropsychological tests measuring all of these functions, in some cases even the same tests as previous studies, but did not find any relationships with WMH lesions. One major reason for these diverse results may be the quantification of WMHs by manual analysis in previous studies. The lack of association in our study may also relate to a lesion load that was too small to be detected in the different cognitive test used. Most of the TBIs were defined as mild, and it has been suggested that WMH lesions must reach a specific threshold to affect cognition (41), since connectivity might be an important factor in explaining cognitive dysfunction and fatigability after TBI(42).

Although TBI-related WMH lesions were not related to neuropsychological test results, one significant relationship between number of lesions and self-assessed fatigue was found. This relationship was however negative, meaning that an increased number of WMH lesions was related to less

fatigue. In contrast, one might believe that increased lesion load within the brain would cause more fatigue. This last notion has however been difficult to prove. Most studies have actually found that the severity of head injury is not related to self-experienced fatigue (43–45). Assessing fatigue after TBI is difficult, and although there are more than 30 self-assessment scales of fatigue, there is no “gold standard” for assessing fatigue after TBI(46). In the present study, we used two commonly used measures, the Fatigue Severity Scale (22) and the Mental Fatigue Scale, (30) which both have shown acceptable psychometric properties. Still, with other measures of fatigue, the result might have been different. It should also be noted that the relationship between number of WMH lesions and self-assessment of fatigue was rather weak, and the results may possibly be an effect of multiple comparisons. Another explanation for the negative relationship might be that patients with more severe injuries may have difficulties with self-awareness, making the self-assessments of fatigue less valid. Future research examining the relationship between WMH lesions and self-experienced fatigue should thus include and adjust for measures of self-awareness.

More than 20% of patients with mild TBI did not have any WMH lesions. Still, they suffered from fatigue and other neuropsychological impairments one or several years after a mild TBI, which usually resolves within months from injury(47). However, studies do show that there are a few cases of mild TBI that do not recover, but instead experience persisting or chronic symptoms (48,49), even though many do not have any objectively verified injuries in radiological examinations(50). Some have even suggested that persisting symptoms after mild TBI may not be related to the brain injury per se, but instead to other factors(51). It is of course reasonable to expect this “miserable minority”(52) to stay in contact with neurorehabilitation centers, thus being possible to include in the present study. It has also been stated that mild TBIs, especially concussions, do not cause structural damage within the brain, but instead affects the functionality of the brain (50). Thus, structural imaging of the brain may not always be suitable in the detection of subtle cognitive impairment or fatigue after TBI. Our study does not contribute to the understanding of why these patients have symptoms but suggests that WMH lesions cannot explain these



symptoms. More studies are needed to investigate the mechanisms behind persisting symptoms in this patient group.

## Limitations

This study has several limitations. First and foremost, the sample is small, especially in the moderate-severe TBI groups, affecting power in all analyses, which can be a contributing factor to the negative results regarding relationships between TBI-related WMHs and neuropsychological performance. Further, the sample is rather heterogenic, both when it comes to TBI severity and time since injury. All patients had favorable outcomes (i.e. GOSE moderate or better recovery), making generalization to patients with less favorable outcome limited. It is also important to note that all patients in the current study were more than one year from injury (mean of more than 8 years). These patients are suffering from persistent symptoms after their brain injury, which means that they are possibly different from patients recovering more quickly, both regarding premorbid (53) and injury-related (48) factors. Thus, the results only generalize to patients in the chronic phase of traumatic brain injury.

## Conclusions

This study shows that WMH lesions are related to suffering a TBI, and that there is an increased WMH lesion load with increased TBI severity. However, in the present study, these TBI-related WMH lesions were not related to performance on neuropsychological tests but number of WMH lesions was negatively related to self-assessment of fatigue.

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