

# Cognitive Sequelae of Diffuse Axonal Injury

Rainer Scheid, MD; Kathrin Walther; Thomas Guthke, PhD;  
Christoph Preul, MD; D. Yves von Cramon, MD, PhD

**Background:** The results of recent studies on cognitive disability after traumatic brain injury–associated diffuse axonal injury (DAI) are inconsistent. In these studies, the diagnosis of DAI relied on cranial computed tomography.

**Objective:** To further clarify the extent and severity of a possibly DAI-associated cognitive impairment by the use of magnetic resonance imaging (MRI) and detailed neuropsychological testing.

**Design and Participants:** From a databank of 299 patients with traumatic brain injury, 18 patients (age range, 17-50 years; median initial Glasgow Coma Scale score, 5) who showed an MRI lesion pattern compatible with pure DAI were identified. All of the patients had undergone MRI on a 3-T system. Pure DAI was defined by the findings of traumatic microbleeds on T2\*-weighted gradient-echo images in the absence of otherwise traumatic or nontraumatic MRI abnormalities.

**Main Outcome Measures:** Neuropsychological performance in the categories of attention and psychomo-

tor speed, executive functions, spans, learning and memory, and intelligence 4 to 55 months (median, 9 months) after traumatic brain injury.

**Results:** All of the patients showed impairments of 1 or more cognitive subfunctions, and no cognitive domain was fundamentally spared. Memory and executive dysfunctions were most frequent, the former reaching a moderate to severe degree in half of the patients. In comparison, deficits of attention, executive functions, and short-term memory were mostly mild. Correlations between the amount of traumatic microbleeds and specific or global cognitive performance were absent.

**Conclusions:** An MRI lesion pattern compatible with isolated DAI is associated with persistent cognitive impairment. The traumatic microbleed load is no sufficient parameter for the assessment of DAI severity or functional outcome.

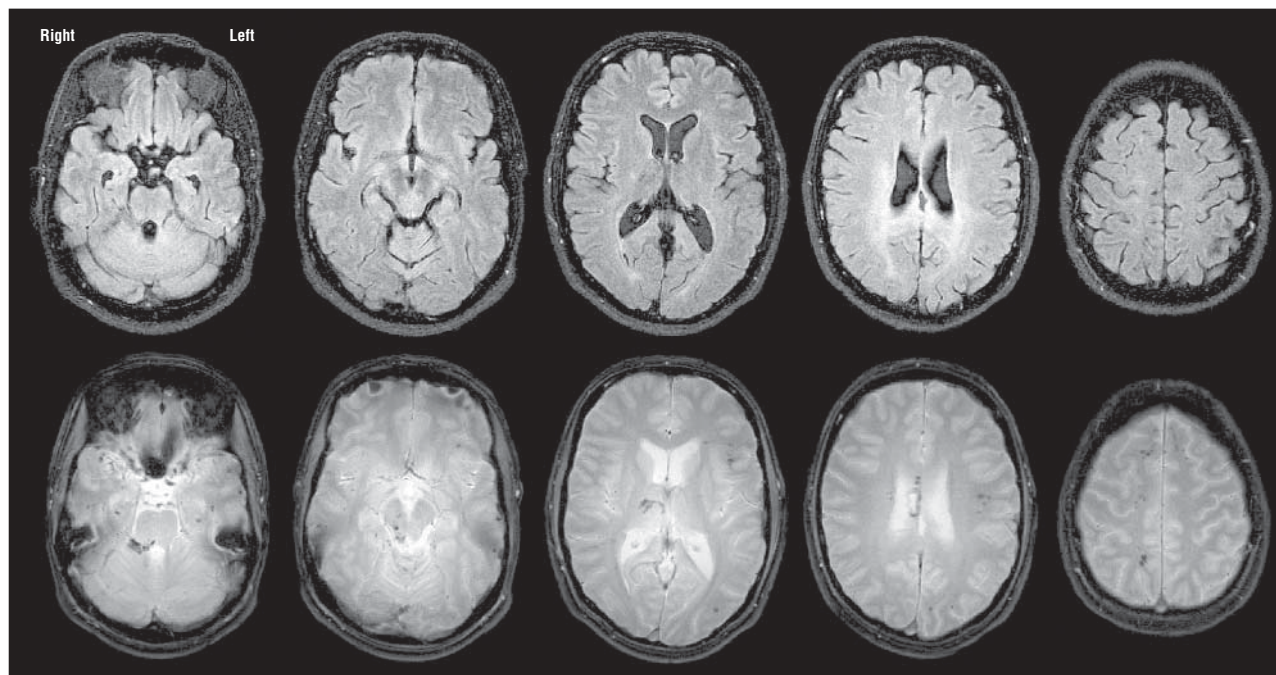
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**Author Affiliations:** Day Clinic of Cognitive Neurology, University of Leipzig (Drs Scheid, Guthke, and von Cramon and Ms Walther) and Max Planck Institute for Human Cognitive and Brain Sciences (Drs Scheid, Preul, and von Cramon), Leipzig, Germany.

**D**IFFUSE AXONAL INJURY (DAI) is a distinct type of primary traumatic brain injury<sup>1-3</sup> (TBI) that has traditionally been associated with poor clinical outcome.<sup>4</sup> However, the results of several studies<sup>5-8</sup> have qualified this view. Wallesch et al<sup>7</sup> found that patients with mild to moderate TBI and DAI mainly had transient deficits of psychomotor speed, verbal short-term memory, and frontal lobe cognitive functions. Another study<sup>8</sup> showed that slowed information processing was related to DAI, but subjects with predominant DAI showed greater recovery over time than those in whom focal lesions were the main abnormality. A most recent study<sup>9</sup> on this issue, however, revealed that patients with probable DAI had long-lasting neuropsychological impairments that were dominated by executive and memory dysfunctions.

In the true sense, DAI is a neuropathologic diagnosis. Therefore, the method that is applied for its *in vivo* assessment is a critical issue. In a previous study,<sup>10</sup> it was shown that T2\*-weighted gradient-echo magnetic resonance imaging (MRI) at high field strength is a useful tool for the evaluation of DAI in the chronic stage of TBI. Due to the neuropathologically proven frequent hemorrhagic component,<sup>1,2</sup> lesions suspicious for DAI appear as small hypointense signal alterations (traumatic microbleeds [TMBs]).

Considering the inconsistent literature, the aim of the current study was to further examine the relevance of DAI for determining outcome by means of detailed neuropsychological testing in a group of patients with TBI whose MRIs showed only TMBs as pathological findings. These patients were therefore considered to have had pure DAI. We hypothesized the following: (1) these patients show chronic cog-



**Figure.** Example of magnetic resonance imaging findings for 1 patient; with comparison between fluid-attenuated inversion recovery images (upper row) and T2\*-weighted gradient-echo images (lower row). Axial-view sections of exactly corresponding levels are shown. Multiple traumatic microbleeds are shown on the T2\*-weighted gradient-echo images. The patient was a 25-year-old driver of a car that collided with a roadworks vehicle on September 28, 2003.

nitive dysfunction; (2) owing to the diffuse character of the underlying brain injury, no specific cognitive domain is predominantly affected; and (3) with respect to the results of a previous study,<sup>10</sup> the number of TMBs does not correlate with overall cognitive performance.

## METHODS

### PATIENTS AND MRI

Eighteen patients (5 women, 13 men; age range, 17-50 years; median age, 22.5 years) with histories of TBI were included in the study. Seventeen patients had closed injuries; in 1 patient, there was suspicion of an open TBI. All of the participants had been inpatients of the Day Clinic of Cognitive Neurology, University of Leipzig, Leipzig, Germany, and were selected from a databank of 299 patients with TBI. Neuroradiologic and psychometric assessment was conducted between June 8, 1996, and May 14, 2004. Magnetic resonance imaging was performed on a 3-T system; the imaging and evaluation protocols have been published previously.<sup>10</sup> In short, the protocol comprised 3 scans of the same geometry (20 slices, axial plane, slice thickness of 5 mm, slice gap of 2 mm): (1) 2-dimensional T1-weighted reduced power multislice modified driven equilibrium Fourier transform images<sup>11</sup> (field of view, 25.0 × 25.0 cm; data matrix, 256 × 256; repetition time, 1.3 seconds; echo time, 10 milliseconds); (2) 2-dimensional T2-weighted fast spin-echo scans (field of view, 25.0 × 25.0 cm; data matrix, 512 × 512; repetition time, 8.5 seconds; echo time, 21.7 milliseconds); and (3) 2-dimensional T2\*-weighted gradient-echo images (field of view, 19.2 × 19.2 cm; data matrix, 256 × 256; repetition time, 700 milliseconds; echo time, 15 milliseconds; flip angle, 25°). In 5 patients, 2-dimensional fluid-attenuated inversion recovery imaging (repetition time, 1000 milliseconds; echo time, 94 milliseconds; inversion time, 2500 milliseconds) was also performed. All of the MRIs were evaluated independently by 2 of us (R.S. and C.P.). Any small (1- to 15-mm) focus without con-

nection to the brain surface and/or the ventricular system that appeared hypointense on both T1- and T2-weighted MRI and/or on T2\*-weighted gradient-echo MRI was defined as a traumatic microbleed (TMB) and was regarded as an MRI correlate of DAI (**Figure**). In each of the 20 patients who were selected for the study, MRI showed TMBs in the absence of otherwise traumatic or nontraumatic MRI abnormalities. The number of TMBs was registered for each individual. No patient had symptoms or signs of preexisting or concomitant medical or psychiatric disorders or a history of a previous TBI. With the exception of 1 patient who had fallen from a substantial height during a mountain hike, all of the patients were victims of road traffic accidents. Injury severity was assessed by the use of the reported Glasgow Coma Scale (GCS) score<sup>12</sup> from initial hospital admission (score range, 3-15; median score, 5). In cases where the GCS score was missing, specific information from the short-term records was used to calculate GCS scores retrospectively. Owing to insufficient information, the GCS score could not be calculated for 5 patients. The duration of loss of consciousness was not analyzed because of the probable interference of standard therapeutic interventions. The median interval between brain injury and neuropsychological testing was 9 months (interval range, 4-55 months). No patient was under continuous psychotropic medication at the time of the psychometric assessment. Demographic and clinical data are summarized in **Table 1**.

### NEUROPSYCHOLOGICAL ASSESSMENT

A variety of neuropsychological tests were used for the evaluation of several cognitive domains. For attention and psychomotor speed, the Test of Attentional Processes (Testbatterie zur Aufmerksamkeitsprüfung) alertness subtest,<sup>13</sup> which measures the simple reaction times for visual presented stimuli and included mean reaction times, variation or stability of reaction, and difference in reaction times after stimulus announcement (phasic alertness) as the test scores, and the Test of Attentional Processes sustained attention subtest,<sup>13</sup> which requires a simultaneous consideration of

**Table 1. Clinical and Demographic Data**

Characteristic	Value
Patients, No.	18
Sex, female/male, No.	5/13
Age, median (range), y	22.5 (17-50)
Time after injury, median (range), mo	9 (4-55)
GCS score, median (range) (n = 13)	5 (3-15)
TMBs, median (range), No.	15.5 (1-104)

Abbreviations: GCS, Glasgow Coma Scale; TMB, traumatic microbleed.

visual and auditory presented stimuli and included mean reaction times, variation or stability of reaction, number of omissions, and errors as the test scores, were used. For executive functions, the Behavioral Assessment of Dysexecutive Syndromes,<sup>14</sup> which measures 6 unstructured tasks reflecting daily living situations that require role shifting, planning, problem solving, and estimation and included the sum score as the test score, and the Stroop Test,<sup>15</sup> which measures the time to read and name color names that are printed in ink incongruous to the written color name and included the time to name the incongruent word as the test score, were used. For learning and retaining, the California Verbal Learning Test,<sup>16</sup> a word list learning test that requires the reproduction of 16 categorized words presented over 5 trails, included subtests for free recall, recall after the presentation of a list of interfering items, delayed recall (20 minutes), and recognition from a list of 44 items, and included the total number of reproduced items during trails 1 to 5 (A1-5), number of reproduced items after the interfering condition (A6), number of reproduced items after the delay (A7), and number of hits and errors in the recognition task as the test scores, and the Wechsler Memory Scale-Revised,<sup>17</sup> the test battery that measures verbal and visual memory performance immediately and after a delay of 30 minutes and included the verbal, visual, and delayed scores as the test scores, were used. For spans, the digit span subtest of the Wechsler Memory Scale-Revised, which involved reproduction of a subset of auditory presented numbers of increasing length in the same order and in the reverse order and included numbers recalled forward and backward as the test scores, and the spatial span subtest of the Wechsler Memory Scale-Revised, which involved replication of an increasingly long series of blocks pointing in the same order or in the reverse order and included the replication of blocks forward and backward as the test scores, were used. For intelligence, the Multiple Choice Vocabulary Test (Mehrfachwahlwortschatztest),<sup>18</sup> which is a vocabulary test in which 1 real word has to be differentiated from 4 alternative nonsense words to estimate the premorbid level of intelligence and which included the number of correct namings as the test score, was used.

Test norms of each test score were used to assess the levels of impairments. Based on the performance data of age- and education-matched healthy controls provided by the test handbooks, raw scores were transferred to  $z$  scores. All of the scores greater than 1 negative SD ( $z > -1$ ) were recoded to  $z_r = 0$ . A test performance between 1 and 2 negative SDs ( $-2 < z < -1$ ) was assigned to  $z_r = -1$ , and a performance beyond 2 negative SDs ( $z < -2$ ) was assigned to  $z_r = -2$ . The  $z$  scores were recoded ( $z_r$ ) because the study focused on the negative impact of DAI and because the heterogeneity of the tests did not allow for the discrimination of the test performance beyond 2 negative SDs for every single test.

To improve reliability, all of the  $z_r$  scores that represent the same cognitive subfunction (attention, executive function, spans, learning, and retention) were averaged to functional scores ( $z_f$ ). These  $z_f$  scores thus represent the degree of impairment in each cognitive subfunction:  $z_f$  scores of 0.0 to -0.2 indicate no impairment;  $z_f$  scores less than -0.2 to -0.6, mild impairment;  $z_f$  scores less than -0.6 to -1.0, moderate impairment; and  $z_f$  scores

less than -1.0, severe impairment. The average of all of the  $z_f$  scores of 1 patient represents his or her overall cognitive state.

As the neuropsychological data were collected in part retrospectively over an interval of 8 years, the applied neuropsychological tests were not congruent for every patient. In 6 patients, missing data were replaced by the individual patient's performance in tests representing comparable subfunctions.<sup>19,20</sup> For example, the Multiple Choice Vocabulary Test score was replaced by the score on the Vocabulary Test (Wortschatztest)<sup>21</sup> (a revised version of the Multiple Choice Vocabulary Test) and educational data. One patient was not able to fulfill the demands of the Test of Attentional Processes divided attention subtest.

## RESULTS

Premorbid intelligence was average or normal in all of the patients. **Table 2** shows the patients' overall performance for each neuropsychological test as compared with healthy controls. As summarized in **Table 3**, patients showed mostly mild attentional deficits and mild executive dysfunctions. Spans were usually preserved or only slightly affected. Memory disturbances were frequent, and in half of the patients, these impairments were moderate to severe. With respect to the individual performance in tests representing a specific cognitive subfunction, cognition was not completely unimpaired in any patients. One third of the patients showed substantial impairments of their cognitive states.

Results of the tested interrelationships between the individual number of TMBs and cognitive performance are shown in **Table 4**. In summary, no significant correlations were found after Bonferroni correction ( $P > .002$ ).

## COMMENT

To our knowledge, our study is the first on a patient population with neuroradiological signs compatible with pure DAI. The diagnosis relied on MRI on a 3-T system, which probably increases the sensitivity for the detection of TMBs.<sup>10,22</sup> With respect to the aforementioned findings, our hypotheses can be answered as follows: (1) An injury pattern that is compatible with pure DAI led to chronic cognitive dysfunction in the majority of patients. With regard to the individual patients' performance in each single test, no patient was completely unaffected. (2) Impairments were verifiable in all of the cognitive domains. Half of the patients showed moderate to severe deficits in learning and retaining new information. In comparison, attention, executive functions, and maintenance of information over a short period were mildly disturbed. Verbal memory was gradually more impaired than visuospatial memory. (3) Neither overall nor specific cognitive impairments were correlated with the individuals' number of TMBs. Therefore, it seems that the number of TMBs is no sufficient parameter for the assessment of the severity of DAI.

## COMPARISON WITH PREVIOUS STUDIES

Our findings do not support the results of a study by Wallesch et al,<sup>7</sup> who found that DAI mainly causes mild

**Table 2. Applied Neuropsychological Tests and Patients' Performance as Raw Scores and Compared With Healthy Controls (z Scores)**

Scale	Patients, No.	Raw Score, Mean (SD; Range)	z Score, Mean (SD; Range)
Multiple Choice Vocabulary Test			
Correct items, No.	15	26.1 (2.8; 21 to 30)	-0.1 (0.5; -0.9 to 0.8)
TAP alertness subscale			
Mean reaction time, sec	18	299.4 (66.9; 202 to 424)	-1.5 (0.8; -2.4 to 0.1)
Variation or stability, sec	18	57.8 (24.3; 30 to 119)	-1.3 (0.7; -2.4 to 0.3)
Phasic alertness	18	0.07 (0.09; -0.09 to 0.25)	0.2 (0.9; -1.5 to 2.5)
TAP divided attention subscale			
Mean reaction time, sec	17	725.8 (93.8; 512 to 897)	-1.4 (0.8; -2.2 to 0.7)
Variation or stability, sec	17	225.2 (73.6; 144 to 432)	-0.4 (0.7; -2.0 to 0.6)
Omission	17	2.9 (2.7; 0 to 10)	-0.7 (1.1; -3.0 to 1.0)
Errors	17	1.4 (2.3; 0 to 10)	0.0 (1.1; -3.0 to 1.0)
BADS			
Sum	18	18.5 (3.1; 11 to 23)	-0.3 (1.4; -4.0 to 1.6)
Stroop			
Time, sec	13	156.2 (29.4; 98 to 215)	-1.5 (1.0; -2.8 to 0.8)
Spans			
Digit span forward	18	5.9 (1.1; 4.0 to 8.0)	-0.3 (1.2; -2.0 to 2.1)
Digit span backward	18	4.8 (1.0; 3.5 to 7.0)	-0.2 (0.8; -1.2 to 1.2)
Block span forward	18	5.6 (0.7; 4.5 to 7.0)	-0.2 (0.8; -1.9 to 0.8)
Block span backward	18	5.0 (0.8; 4.0 to 6.5)	-0.8 (0.8; -2.0 to 0.7)
CVLT			
Recalled items A1-5	18	48.1 (11.8; 22 to 63)	-1.7 (1.7; -4.5 to 0.6)
Recalled items A6	18	8.4 (3.3; 2 to 14)	-2.4 (1.8; -5.0 to 1.0)
Recalled items A7	18	9.5 (4.1; 2 to 15)	-2.0 (1.9; -5.0 to 1.0)
Recognition hits	18	14.6 (1.9; 8 to 16)	-1.1 (1.6; -5.0 to 1.0)
False positive	18	1.1 (2.0; 0 to 7)	-0.4 (0.9; -3.0 to 0.0)
WMS			
Verbal subscale, raw score	18	69.8 (17.9; 40 to 90)	-0.9 (1.3; -3.1 to 1.2)
Visual subscale, raw score	18	57.3 (6.0; 44 to 67)	-0.2 (1.0; -2.3 to 1.5)
Delay subscale, raw score	18	77.5 (12.7; 56 to 103)	-0.8 (1.3; -2.8 to 1.5)

Abbreviations: BADS, Behavioral Assessment of Dysexecutive Syndromes; CVLT, California Verbal Learning Test; TAP, Test of Attentional Processes; WMS, Wechsler Memory Scale-Revised.

**Table 3. Frequency and Levels of Impairment With Respect to the Tested Cognitive Subfunctions and an Overall Cognitive Score (z Scores)\***

Cognitive Subfunction	Unimpaired, No. (%)	Mild Impairment, No. (%)	Moderate Impairment, No. (%)	Severe Impairment, No. (%)	Cognitive Score, Mean (SD; Range)
Attention	4 (22)	9 (50)	2 (11)	3 (17)	0.55 (0.46; 0.00-1.57)
Executive functions	4 (22)	7 (39)	4 (22)	3 (17)	0.67 (0.51; 0.00-1.50)
Spans	8 (44)	8 (44)	1 (6)	1 (6)	0.24 (0.33; 0.00-1.25)
Learning and retaining	4 (22)	5 (28)	5 (28)	4 (22)	0.67 (0.54; 0.00-1.63)
Cognitive score	1 (6)	11 (61)	4 (22)	2 (11)	0.57 (0.35; 0.07-1.45)

\*Unimpaired indicates z greater than -0.20; mild impairment, z greater than -0.60; moderate impairment, z between -0.60 and -1.0; severe impairment, z less than -1.0.

and transient neuropsychological deficits. In particular, the high prevalence of memory dysfunctions in our study is contrary to that in previous articles<sup>6,7</sup> but matches with the findings of a more recent study performed by Wallesch and colleagues.<sup>9</sup> There are several possible explanations for these discrepancies.

First, there are differences in the patient population with respect to TBI severity. The median GCS score in the earlier study by Wallesch et al<sup>7</sup> was 14.0, which corresponds to mild TBI.<sup>12</sup> The median GCS score of our patients was 5.0, which corresponds to severe TBI. In the study by Felmingham et al,<sup>8</sup> the mean GCS scores were 9.5 for the group with a mixed lesion pattern and 5.0 for the diffuse

group. Because TBI-related cognitive impairments should depend in part on TBI severity, at least quantitative differences among the study results should be expected. In this respect, it is particularly interesting to note that the mean GCS score of the patients with DAI in the most recent study by Wallesch et al<sup>9</sup> was 6. As mentioned before, these patients showed persistent neuropsychological impairments.

Second, the previous studies<sup>6-8</sup> and our study follow different designs. The former compared 2 groups of patients with TBI with different injury patterns and did not include references to normal subjects. Because only raw scores are imparted, there is no information about the severity of impairments. This procedure only allows for

**Table 4. Spearman Rank Correlations Between the Results of the Various Neuropsychological Tests and Traumatic Microbleeds**

Neuropsychological Test	Patients, No.	Spearman $\rho$	Sign*
Cognitive score	18	0.12	0.64
Attention	18	0.20	0.42
Executive functions	18	0.16	0.52
Spans	18	0.15	0.55
Learning and retaining	18	-0.02	0.94
TAP alertness subscale, sec			
Mean reaction time	18	0.09	0.72
Variation or stability	18	0.18	0.48
Phasic alertness	18	0.46	0.06
TAP divided attention subscale, sec			
Mean reaction time	17	0.08	0.75
Variation or stability	17	0.07	0.79
Omission	17	0.02	0.94
Errors	17	0.18	0.49
Spans			
Digit span forward	18	0.12	0.64
Digit span backward	18	0.13	0.16
Block span forward	18	0.34	0.17
Block span backward	18	-0.05	0.85
BADS			
Sum	18	-0.06	0.83
Stroop			
Time	13	0.20	0.52
CVLT			
Trails A1-5	18	0.06	0.82
Trail A6	18	-0.07	0.79
Trail A7	18	0.01	0.98
Hits	18	-0.22	0.39
False positive	18	-0.05	0.84
WMS			
Verbal subscale, raw score	18	0.34	0.17
Visual subscale, raw score	18	0.34	0.17
Delay subscale, raw score	18	0.28	0.27
Multiple Choice Vocabulary Test			
Correct items, No.	15	-0.54	0.04

Abbreviations: BADS, Behavioral Assessment of Dysexecutive Syndromes; CVLT, California Verbal Learning Test; TAP, Test of Attentional Processes; WMS, Wechsler Memory Scale-Revised.

\*Significance after Bonferroni correction is  $P < .002$ .

conclusions about whether one group is more impaired than the other. However, we believe that a comparison with normal data is more appropriate for the evaluation of the impact of DAI on cognition. In our study, patients' performances were therefore correlated with data from age-matched healthy controls, and thus there is no need for a control group. A further critical issue is the difference in the selection of memory tests. Not all of the previously used tests are sufficient for the evaluation of memory in detail. In the first study by Wallesch et al,<sup>6</sup> a test that is normally used for the assessment of dementia was included. The tests in their second study<sup>7</sup> were suitable for the assessment of short-term memory only, and the retention and retrieval of information over longer intervals were neglected. Our results indicate that retention over the short term is particularly spared in patients with TBI with isolated DAI.

Third, the majority of the aforementioned studies were performed with patients with mixed lesion patterns, ie,

a combination of different degrees of focal cortical contusions plus possible DAI.<sup>5-8</sup> This is a major limitation of these studies, as it hampers the drawing of conclusions about the selective impact of DAI.

Fourth, in the previous studies, cranial computed tomography was used for the classification of TBI and the diagnosis of DAI. However, compared with MRI, cranial computed tomography is of insufficient sensitivity for this purpose.<sup>10,23</sup> In this context, it should be remembered that DAI was temporary, in part even defined negatively by the presence of coma without abnormal cranial computed tomographic results.<sup>5,24</sup>

Fifth, the first of the studies by Wallesch et al<sup>6</sup> as well as the study by Felmingham et al<sup>8</sup> were performed in the acute and postacute stages of TBI. Their results thus leave the question of possible long-term cognitive sequelae of DAI unanswered.

Although impairments of executive functions were mainly mild in our patients, many relatives described distinct abnormalities in activities of daily living. Similar observations have already been described by other investigators.<sup>25,26</sup> Many of the dysexecutive tests lack sufficient sensitivity for the prediction of handicaps and impairments that will probably occur in everyday life. The finding of mild attentional deficits in many of our patients confirms previous observations of frequent impairments of attentional processing in DAI.<sup>5,7,8</sup> However, with respect to the specific performance on single tests, the deficits seem to be attributed to a reduction of basic speed processing more than to difficulties in higher-order attentional processes.

We did not find significant interrelationships between impairments of attention, executive functions, and memory. Nevertheless, we assume the latter to be, in part, a consequence of disturbed working-with-memory capacities.<sup>27</sup> The assumption of a reduced use of organizational strategies fits well into our previous finding that TMBs are localized in the frontal lobes in the first line<sup>10</sup> and may thus predominantly lead to the disruption of frontosubcortical circuits. However, since TMBs were second most frequently situated in the temporal lobes in that study, the disruption of memory-related circuits is also likely, and a genuinely temporal component of the mnemonic dysfunction in DAI must also be assumed. The findings of memory deficits in patients with DAI can therefore not solely be interpreted in terms of an executive dysfunction, as was suggested by Fork et al.<sup>9</sup> Furthermore, the failure to verify statistically significant interrelationships may be explained at least in part by the different levels in sensitivity of the applied neuropsychological tests.

#### TMB LOAD AND COGNITIVE PERFORMANCE

Although cognitive outcome was assessed by means of detailed neuropsychological testing, there was no correlation with the number of TMBs. This is similar to the results of the previous study<sup>10</sup> in which outcome was assessed by the use of the extended Glasgow Outcome Scale.<sup>28</sup> The controversial relationships between MRI abnormalities and cognitive states are also being discussed in other disorders that are characterized by diffuse involvement of the white matter, eg, in cerebral small vessel disease.<sup>29-34</sup> Reported correlations seem to be weak at

best. Our finding of a lacking correlation between the TMB load and cognitive performance is therefore not surprising. Within the spectrum of possible explanations, we favor the following: (1) the specific distribution of TMBs may be more important than their overall amount, and (2) there is no information about the structural and functional integrity of nerve fibers within a TMB and the grade of disruption of functional circuits that it may lead to. The TMBs can therefore be considered only a diagnostic but not functional parameter of DAI.

### LIMITATIONS OF OUR STUDY

We did not perform serial neuropsychological testing or imaging. Different from the aforementioned studies,<sup>7,9</sup> we therefore cannot comment on the course of cognitive impairment or recovery after DAI. Moreover, in the majority of patients, the psychometric data were collected retrospectively. By definition, retrospective data are of minor validity. However, owing to the relative rareness of pure DAI (18 [6%] of the 299 patients with TBI in our population), a prospective study with a sufficient sample size would be time-consuming, at least in a single-institution approach. An additional source of probable bias is the study setting. Our patient population is highly selected. On one hand, we might have missed patients with full recovery who did not seek further medical support despite having DAI. On the other hand, we probably did not include patients with more severe deficits who were not suitable for treatment in a day clinic. Finally, in 4 patients, the neuropsychological testing was conducted within the first 6 months after TBI (4 months after TBI in 1 patient and 5 months after TBI in 3 patients) and hence possibly prior to having reached a stable cognitive deficit. However, a subgroup analysis in these patients did not reveal significant differences as compared with subjects with longer post-TBI intervals.

### CONCLUSIONS

Magnetic resonance imaging abnormalities compatible with pure DAI are associated with chronic dysfunctions, particularly focusing on executive functions and memory. The appearance of TMBs on MRIs is important for the correct diagnosis but is in itself no sufficient parameter for the estimation of injury severity or outcome of DAI, which must be based on clinical and functional assessments. In this respect, future studies will have to clarify the role of TMB location and the usefulness of supplementary imaging methods (such as diffusion-weighted imaging, diffusion tensor imaging, magnetization transfer imaging, and susceptibility-weighted imaging).<sup>35-38</sup>

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**Correspondence:** Rainer Scheid, MD, Day Clinic of Cognitive Neurology, University of Leipzig, Liebigstrasse 22a, 04103 Leipzig, Germany (scheid@cbs.mpg.de).

**Author Contributions:** *Study concept and design:* Scheid, Walther, Guthke, and von Cramon. *Acquisition of data:* Scheid, Walther, and Preul. *Analysis and interpretation of data:* Scheid, Walther, Guthke, Preul, and von Cramon.

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#### Announcement

**Trial Registration Required.** In concert with the International Committee of Medical Journal Editors (ICMJE), *Archives of Neurology* will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as <http://ClinicalTrials.gov>). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorial by DeAngelis et al in the January issue of *Archives of Dermatology* (2005;141:76-77). Also see the Instructions to Authors on our Web site: [www.archneurol.com](http://www.archneurol.com).