Journal id: TBIN_A_130945

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NO QUERIES

Brain Injury, Month?? 2005; 0(0): 1–10

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Central executive system impairment in traumatic brain injury

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(Received 10 December 2004; accepted 11 August 2005)

Abstract

Primary objective: This study investigated whether cognitive impairment after traumatic brain injury (TBI) can be considered a consequence of (1) a speed processing deficit or (2) an impairment of the Central Executive System (CES) of working memory.

Methods and procedures: Thirty-seven TBI patients underwent a standardized battery of neuropsychological tests evaluating speed processing, sustained attention, short-term memory, working memory, divided attention, executive functions and long-term memory.

Main outcomes and results: Patients showed severe deficits in working memory, divided attention, executive functions and long-term memory. Divided attention, long-term memory and executive functions deficits significantly correlated with working memory, but not with speed processing deficits. Moreover, multiple regression analyses showed that a CES impairment and not a speed processing deficit predicted divided attention, executive functions and long-term memory deficits. The severity and the site of brain lesions did not predict the level of CES or speed processing impairment.

Conclusions: The cognitive impairment following TBI seem to be caused by an impairment of the Central Executive System, rather than a speed processing deficit.

Keywords: *Traumatic brain injury, central executive system, attentional and memory disorders*

Introduction

Attention, memory and executive functions are often impaired after traumatic brain injury (TBI). Some authors showed slower reaction times (RTs) to target stimuli in patients with TBI compared to normal controls [1–3] and also deficits in working memory (WM) [4], divided attention [4–8], executive functions [9–12] and long-term memory (LTM) [13–17].

Some investigators proposed that cognitive deficits subsequent to TBI emerge as a consequence of a speed processing deficit, that is a general slowing of perceptual, motor and cognitive sub-routines affecting information processing (speed processing hypothesis). This 'slowness' effect seems to be more evident when task load increases and more attentive resources and executive control are required, as in divided attention and executive functions tasks [1, 3, 18]. Thus, according to these authors, differences in cognitive performance between patients with TBI and normal controls do not indicate the presence of an impairment in any specific function, but are due to the general slowing in information processing.

Several lines of evidence favouring the 'speed processing deficit' hypothesis have been identified. First, patients with TBI perform a variety of tasks more slowly than controls and this effect is greater in choice than in simple RT tasks [19]. Secondly, in some cases, differences between patients and controls in RTs on divided attention tasks disappeared when differences in single RTs tasks were controlled by using covariate analyses [1]. Thirdly, in investigating executive functions by means of the 'Tower of London' test, some authors found a slower execution

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ISSN 0269–9052 print/ISSN 1362–301X online
DOI: 10.1080/02699050500309627

time in patients with TBI compared to normal controls, but a normal score in other parameters evaluating planning abilities [1]. Therefore, they concluded that executive functions deficits in patients with TBI are best explained by a speed processing deficit rather than by planning deficits [1]. The aforementioned studies support the idea that, in patients with TBI, low divided attention and executive functions performance might be secondary to a speed processing deficit.

A quite different account of divided attention and executive functions deficits has been proposed by other authors [4, 5]. According to them, functional deficits after TBI are due to an impairment of the central executive system of working memory (WM hypothesis).

Working memory is a limited capacity system that temporarily maintains and elaborates information and supports human thought processes by providing an interface between perception, long-term memory and action [20]. This model has three major components: two slave systems and a Central Executive System (CES). Separate slave systems are responsible for temporarily storing verbal and non-verbal information, while the CES processes information in WM. The CES is also supposed to be involved in regulating the distribution of limited attentional resources in divided attention conditions. Moreover, in analogy with the Supervisory Attentional System [21], CES co-ordinates cognitive functions when unusual tasks have to be performed and, thus, it is supposed to be implicated in problem-solving. Finally, the CES is supposed to have a role in deep processing and strategic organization of information to be stored in LTM [20, 22]. According to the WM hypothesis, neuropsychological impairments found in TBI patients could be explained by a CES impairment, since this system seems to be involved in various cognitive domains, such as WM, divided attention, executive functions and LTM.

The first aim of the present study was to investigate whether cognitive deficits following TBI mainly depend on speed processing deficits or a CES impairment.

According to the WM hypothesis, patients with WM deficits should also have deficits in functions depending on CES functioning, i.e. divided attention, executive functions and LTM. Concerning LTM, a more specific hypothesis can be put forward. It is well established that human memory relies on several distinct processes, namely encoding, storage and retrieval [23]. Encoding refers to the initial processing and acquisition of the information to be learned, whereas storage and retrieval refer to the processes of maintaining and recovering previously acquired information. Since a specific role of the CES during encoding has been hypothesized [20, 22], a CES impairment should cause deficits in encoding rather than in maintaining or recalling information.

The second aim of the present study concerns the relationship between the characteristics of brain lesions (size and site) and the severity of CES impairments and speed processing deficits. The severity of brain injury has shown to predict neuropsychological outcome in TBI: it has been found that patients who had no visible lesions on CT scans were characterized by an enhanced performance in several neuropsychological tests relative to patients with mass lesions or severe diffuse injuries [24]. Thus, in order to investigate in more detail whether the severity of brain lesions predicted the degree of CES and speed processing deficits, the level of performance in both functions was compared among groups of patients presenting lesions of different severity.

Additionally, the locus of the brain lesion in TBI can shed some light on the neural substrate of the WM impairment. Recent neuroimaging and clinical evidence suggests a strict link between CES functioning and the frontal cortex [21, 25–31]. On the basis of these findings it should be expected that patients presenting frontal lobe lesions are more impaired in tasks tapping CES functioning than patients with lesions affecting other brain areas. To investigate this hypothesis, WM performance of patients with injuries involving the frontal lobes was compared with that of patients with injuries in other brain areas.

On the other hand, no specific hypothesis concerning the role of the site of the lesion in predicting speed processing deficits has been put forward. Indeed, speed processing is not considered a specific cognitive function with a clear neural substrate, but rather a resource emanating from the activity of a global neural network. Thus, a slowness in information processing is supposed to be a common effect of general brain damage rather than a lesion in specific brain areas [3].

Material and methods

Subjects

A sample of 64 patients, resident in Cesena, who were admitted to the Bufalini Hospital (Cesena) for TBI in the last 7 years were re-contacted for the present study. All of them underwent a neurological examination. Time from TBI was at least 4 months. Patients were selected for participating in the study if they complained of lack of attention, poor memory or loss of efficiency in everyday life. Exclusion criteria were prior history of TBI or other

Table I. Patients' clinical and demographic details. Demographic and clinical data are expressed according to gender, age, level of education, severity of trauma (Glasgow Coma Scale (GCS) >12 = mild; 9–12 = moderate; <9 = severe), time post-injury and severity of brain lesions according to Marshall's method [33] (DI = Diffuse Injury I; DII = Diffuse Injury II; EML = Evacuated Mass Lesion; NA = not available CT/MRI scans).

Case	Gender	Age (years)	Education (in years)	Severity of trauma (GCS)	Time post-injury (months)	Severity of lesions
GN	M	24	12	3	12	DII
AB	M	63	5	5	10	NA
AG	F	15	9	8	15	DI
AP	M	54	15	7	13	NA
AV	M	31	13	9	14	DII
BS	M	27	12	6	11	NA
CN	M	49	10	15	17	DII
CP	M	65	11	10	4	DI
DS	M	16	8	5	22	DII
EM	M	63	6	15	8	EML
FB	M	28	8	13	4	DII
FT	M	67	3	15	19	DII
GB	M	69	5	9	16	DII
GG	M	14	9	10	4	DI
GR	M	53	8	5	8	DI
GS	M	51	11	14	7	DII
LC	F	47	13	8	23	DII
LF	F	63	8	15	8	EML
LG	F	23	13	13	12	DII
LO	M	21	8	12	14	NA
LS	F	20	13	3	19	DI
LT	M	58	5	15	22	NA
MA	M	25	12	15	61	DII
MB	M	16	11	14	21	DII
MM	M	18	12	4	8	DI
MR	F	65	5	6	7	EML
MS	F	33	8	15	22	DII
OV	M	34	8	3	15	DII
PA	F	33	17	7	4	DII
PS	M	63	17	15	15	NA
RM	F	29	8	7	78	EML
SC	M	49	8	8	13	NA
SG	F	44	16	6	32	DI
SL	M	41	8	5	20	EML
SS	F	30	18	15	9	DII
SU	M	32	18	6	5	NA
VR	M	57	13	15	20	DII

neurological disease, neuropsychiatric illness or communication problems. Thirty-seven patients participated in the study. Patients gave their informal consent to participate in the study according to the Declaration of Helsinki (BMJ 1991;302:1194) and the local Ethical Committee.

The sample included 26 males and 11 females, whose mean age was 40 years (range 14–67) and mean level of education was 10 years (range 3–18). The mean time that had elapsed between the date of the injury and the date of the neuropsychological examination was 16 months (median time post-injury = 14 months, range = 4–78). The severity of the trauma was evaluated by using the Glasgow Coma Scale at the time of admission (GCS) [32]. According to the GCS, patients were classified as mild (14 patients), moderate (five patients) and severe (18 patients). Patients's details are reported in Table I.

Neuroimaging data

A neuroradiologist, expert in TBI, classified patients' CT/MRI scans for severity of lesions into one of the following categories, according to the Marshall's method [33]: (1) Diffuse Injury I: intra-cranial pathology no detectable at the CT/MRI scan; (2) Diffuse Injury II: cisterns present, with midline shift <5 mm and high or mixed density lesions <25 cc.; (3) Diffuse Injury III with swelling and IV with shift: cistern compressed or absent,

mid-line shift, high or mixed density lesions >25 cc.; (4) Evacuated Mass lesion: High or mixed-density lesion >25 cc.

Neuroimaging data were available for 29 patients: seven patients presented no detectable lesions at CT/MRI scans (group N; see Diffuse Injury I), 17 presented diffuse injuries type II (group D) and five presented evacuated mass lesions (group M).

Lesion location was clinically assessed by an expert neuroradiologist. Among patients with visible injuries (i.e. Diffuse Injury II and Evacuated Mass Lesion), 13 patients presented lesions affecting mainly the frontal lobe (group F) and nine patients presented temporal, parietal and sub-cortical lesions (group NF) (see Table I).

Neuropsychological assessment

To assess speed processing, 'Alertness' sub-test from the Testbatterie zur Aufmerksamkeitsprufung (TAP [34]; Italian version and normative data were taken from Zoccolotti et al. [35]) was used. This test measures reaction times (RTs) with or without a warning signal. Subjects were requested to press a button as rapidly as possible at the appearance of target stimuli in the middle of the computer screen. There were four blocks of trials, for a total of 80 trials. Mean RTs to stimuli presented without a warning were used as a measure of speed processing performance.

In order to evaluate *WM*, the 'Working memory' sub-test from TAP [34, 35] was used. This sub-test consisted in an n-back task, more precisely a 2-back task. In this task, a randomly ordered sequence of 100 digits appeared in the middle of a computer screen at the rate of one stimulus every 3 seconds. Subjects were requested to press a button whenever the presented digit matched the stimulus 2 positions back in the sequence. Fifteen target stimuli were given. The sum of omissions and false reactions was adopted as a measure of WM performance.

Sustained attention was evaluated by using the 'Optical vigilance' sub-test from TAP [34, 35]. In this task, a bar moved up and down with a 1.8 cm oscillation in the centre of the computer screen. Subjects were requested to press a button whenever the bar showed a larger oscillation. The test lasted 10 minutes and the target rate was about one stimulus per minute, for a total of 10 targets. The number of omissions was adopted as an index of sustained attention performance, since it has been demonstrated to be highly reliable [7].

To assess divided attention, the 'Divided Attention' sub-test from TAP [34, 35] was used. In this test, two simultaneous tasks, one visual and one acoustic, were administered. With regard to the visual task, a series of 10×10 cm matrices were displayed on a computer screen, each for 2 seconds. A matrix consisted of an array of dots, with seven 'X's randomly superimposed over them. Subjects were requested to press a button whenever four 'X's formed a square. On the acoustic task, subjects listened to a continuous series of a high tone followed by a low tone and were requested to press a button whenever a repetition of two identical tones occurred. Thirty targets were given (15 acoustic and 15 visual). As measure of divided attention performance, the number of omissions was taken into account, since it has been demonstrated to have the highest reliability [7].

To assess short-term memory, the Digit Span [36], that is supposed to assess the WM slave systems' level of functioning, was used.

Long-term memory was assessed by using the Buschke-Fuld Test [36, 37]. Three scores were considered to evaluate different aspects of LTM performance:

1. Long-term memory retrieval (LTR), i.e. the total number of words recalled—even if they were not constantly produced across all the trials—and, therefore, successfully encoded in long-term memory. This measure is supposed to assess acquisition abilities [36].
2. Consistent long-term retrieval score (CLTR), i.e. the number of words which were repeatedly recalled without need for further reminding until the last trial. This measure assesses storage abilities [37, 38].
3. Delayed free recall score (DFR), i.e. the number of words produced in the delayed free recall task. This measure assesses the retrieval of information from LTM [36].

In order to evaluate executive functions, the Tower of London test was used, according to the procedures and the normative data by Culbertson and Zillmer [39]. The 'total move score', i.e. the number of moves executed by the subject minus the minimum number of solution moves, was used as an index of executive performance.

Results

Incidence of cognitive deficits in patients with TBI

Mean raw scores obtained by patients in each cognitive function are reported in Table II. Scores were corrected for age and level of education, according to the relative normative data [35, 36, 39] and converted into percentile values. A percentile value <5 indicated a pathological performance, a percentile value between 6–10 a borderline performance and a percentile value >10 a normal performance. The frequency of patients showing

pathological, borderline and normal performance for each cognitive function is presented in Table III.

The results indicate that WM is the most impaired function in patients affected by TBI, followed by an impairment in speed processing. Indeed, 62% of patients reported severe deficits in WM and 46% presented highly pathological RTs. It is worth noting that 25% of patients presented both WM and speed processing deficits, 34% of cases presented WM without speed processing deficits and 22% of cases reported speed processing deficits without WM deficits, indicating that the two deficits might be dissociated in patients with TBI. Moreover, it was found that divided attention and executive functions are also frequently impaired, being severely compromised in ~40% of cases. Concerning LTM, a higher percentage of patients reported severe deficits in a measure of acquisition (LTR; 22%) and storage (CLRT; 34%) rather than of delayed recall (DFR; 11%). In contrast, only a few patients obtained pathological scores in short-term memory and sustained attention tasks.

Pearson correlation analyses (performed on raw data) showed that the length of time from injury did not correlate with the results obtained by patients in the investigated cognitive functions.

Table II. Patients' scores. The table reports the descriptive statistics (mean and standard deviation) of the raw scores obtained by patients as a group in the cognitive functions investigated.

	M	SD
Working memory	9.3	8.1
Speed processing (ms)	331	147
Divided attention	3.1	4.4
Executive functions	40	21
Long term memory—acquisition	99	46
Long term memory—storage	60	44
Long term memory—delayed recall	6.8	2.4
Sustained attention	1.00	0.98
Short term memory	4.9	1.3

Correlations among cognitive deficits

In this section, correlations among cognitive deficits have been investigated, by using Pearson correlation analyses. In particular, it was investigated whether divided attention, executive functions and LTM deficits correlated with both WM and speed processing performance. Raw scores were used in the analyses.

The results showed that WM performance correlates with divided attention ($r = 0.60; p < 0.01$), executive functions ($r = 0.53; p < 0.01$), acquisition ($r = -0.50; p < 0.01$), storage ($r = -0.36; p < 0.01$) and delayed recall ($r = -0.37; p < 0.05$). Executive functions correlated with divided attention ($r = 0.58$; $p < 0.01$) and delayed recall ($r = -0.34; p < 0.05$), but not with acquisition ($p = 0.16$) or storage ($p = 0.15$). Divided attention performance correlated with acquisition ($r = -0.44; p < 0.01$) and with delayed recall ($p = -0.49$; $p < 0.01$), but not with storage ($p = 0.11$).

In contrast, no significant correlation emerged between speed processing and divided attention ($p = 0.87$), executive functions ($p = 0.21$), acquisition ($p = 0.27$), storage ($p = 0.37$) and delayed recall ($p = 0.21$).

These results indicate that WM, divided attention, executive functions and LTM deficits are associated to each other, representing a pattern of symptoms after TBI.

To further investigate whether a CES impairment or speed processing deficits accounted for impairments in all these cognitive functions, five linear multiple regression analyses were performed, taking WM and speed processing performance as independent variables and divided attention, executive functions, acquisition, storage or delayed recall as dependent variables. As storage performance depends on the amount of acquired information, the multiple regression analysis of WM and speed processing on storage performance was controlled

Table III. Patients' cognitive profile. The table reports, for each cognitive function, the percentage of patients presenting a pathological performance (percentile value <5), a borderline performance (percentile value between 6–10) and a normal performance (percentile value >10).

	Pathological performance (% of cases)	Borderline performance (% of cases)	Normal performance (% of cases)
Working memory	62	11	27
Speed processing	46	3	51
Divided attention	41	14	45
Executive functions	41	16	43
Long-term memory—acquisition	21	24	55
Long-term memory—storage	34	3	63
Long-term memory—delayed recall	11	37	52
Sustained attention	8	19	73
Short-term memory	17	23	60

for initial acquisition, by entering it as an independent measure in the analysis. For the same reason, the multiple regression analysis on delayed recall performance was controlled for storage effect.

The influence of other parameters, such as age, education, severity of trauma (GCS) and time post-injury on the dependent variables was controlled by entering them as independent measures in the multiple regression analyses.

The results showed a significant effect of WM performance on divided attention ($R^2 = 0.59$; $\beta = 0.81$; $p < 0.001$), whereas no effect of speed processing was found ($p = 0.53$). As far as executive functions are concerned, it was found that WM ($R^2 = 0.42$; $\beta = 0.69$; $p < 0.005$), contrary to speed processing ($p = 0.29$), had a significant influence on performance. Regarding LTM processes, a significant effect of WM was found on acquisition abilities ($R^2 = 0.40$; $\beta = -0.40$; $p < 0.05$), but not of speed processing ($p = 0.36$).

As expected, storage abilities mainly depended on initial acquisition ($R^2 = 0.84$; $\beta = 0.80$; $p < 0.001$), whereas no effect of WM ($p = 0.95$) and speed processing ($p = 0.43$) emerged. Age ($\beta = -0.33$; $p < 0.01$) and severity of trauma at the admission ($\beta = 0.24$; $p < 0.05$) significantly predicted storage abilities. Finally, delayed recall significantly depended on the amount of stored information, i.e. storage ($R^2 = 0.52$; $\beta = 0.66$; $p < 0.005$), but also on WM ($\beta = -0.37$; $p < 0.05$). In contrast, no effect was found of speed processing on delayed recall ($p = 0.13$).

No significant influence of age, level of education, severity of trauma or time since injury emerged in any of the previous analyses, with the exception of an effect of age and severity of trauma on storage abilities (see Table IV).

Table IV. Linear regressions models. The table reports the linear regression models relative to divided attention, executive functions and long-term memory (LTM)—acquisition, storage and delayed recall.

Dependent variable	R^2	β	F	t	p-value
Executive functions	0.42		2.35		0.05
Working memory		0.69		3.4	0.003
Speed processing		0.23		1.1	0.29
Age		0.77		0.3	0.70
Education		−0.04		−0.02	0.82
Time post-injury		0.26		1.41	0.17
GCS		−0.14		−0.71	0.48
Divided attention	0.59		4.37		0.007
Working memory		0.81		4.7	0.001
Speed processing		0.11		0.63	0.53
Age		−0.05		−0.32	0.75
Education		−0.06		−0.42	0.67
Time post-injury		−0.03		−0.23	0.81
GCS		−0.01		−0.1	0.53
LTM-acquisition	0.40		2.16		0.05
Working memory		−0.40		−2.30	0.05
Speed processing		−0.20		−0.93	0.36
Age		−0.36		−1.82	0.08
Education		0.19		1.02	0.31
Time post-injury		0.10		0.52	0.60
GCS		−0.01		−0.03	0.97
LTM-storage	0.84		56.27		0.0001
Acquisition		0.80		6.6	0.0001
Working memory		−0.007		−0.05	0.95
Speed processing		−0.09		−0.80	0.43
Age		−0.33		−2.9	0.009
Education		−0.19		−1.93	0.07
Time post-injury		−0.22		−2.03	0.06
GCS		0.24		2.22	0.04
LTM-delayed recall	0.52		26.8		0.0001
Storage		0.66		3.4	0.003
Working memory		−0.37		−2.1	0.04
Speed processing		−0.29		−1.5	0.13
Age		0.11		0.57	0.57
Education		0.09		0.66	0.51
Time post-injury		−0.04		−0.26	0.79
GCS		0.08		0.52	0.60

Injury severity and cognitive impairment

The relationship between injury severity, as assessed by GCS, time post-injury and cognitive deficits was studied by means of bivariate correlations. GCS score did not correlate with speed processing ($r = 0.16$; $p = 0.41$), WM ($r = -0.14$; $p = 0.5$), divided attention ($r = -0.08$; $p = 0.7$), executive function ($r = -0.08$; $p = 0.69$), initial acquisition ($r = 0.16$; $p = 0.43$), storage ($r = -0.04$; $p = 0.85$) or delayed recall ($r = 0.04$; $p = 0.85$), meaning no relation between trauma severity and patients' long-term cognitive outcome. Moreover, GCS was not correlated with time post-injury ($r = 0.2$; $p = 0.28$), suggesting that patients suffering from a more severe TBI did not complain about cognitive deficits more than patients with less severe TBI.

It is argued that the lack of correlation between trauma severity and patients' long-term outcome may be due, at least in part, to the sensitivity of the GCS. It is worthwhile to remember, indeed, that the GCS score, when evaluated at the admission, can be easily influenced by other factors than trauma severity, such as for example the effect of drugs or alcohol; for this reason GCS not always reflects trauma severity.

Brain lesions and cognitive impairment

Severity of lesion and degree of CES and speed processing impairment. In order to investigate the relation between the severity of brain lesions and the degree of CES impairment and speed processing deficits, WM and speed processing performance were compared among patients presenting lesions of different severity. Three groups of patients were

compared: patients with evacuated mass lesions (group M), patients with diffuse injuries type II (group D) and patients with no detectable lesions at CT/MRI scans (group N).

Two ANCOVAs were performed taking WM or speed processing performance as dependent variable and group as factor, with three levels (groups N, D and M). The influence of other parameters, such as age, level of education, length of time from injury and severity of trauma (GCS) on the dependent variables was controlled by including them as covariates.

The ANCOVA with WM as dependent variable showed no significant effect of group ($p = 0.30$), age ($p = 0.69$), education ($p = 0.63$), time post-injury ($p = 0.51$) or severity of trauma ($p = 0.54$) on performance. Thus, although patients with no detectable brain lesions reported a lower number of errors in the WM task (group N; 5.1) relative to patients with diffuse (group D; 11.6) or mass lesions (group M; 9.5), these differences were not significant.

Likewise, the same ANCOVA conducted on speed processing scores showed no effect of group ($p = 0.66$), age ($p = 0.30$), level of education ($p = 0.99$), time since injury ($p = 0.62$) or severity of trauma ($p = 0.90$) on performance. Thus, RTs of patients with more severe lesions (group M; 335 ms) were not significantly different from those of patients with less severe lesions (group D; 284 ms) or with no detectable lesions (group N; 321 ms).

Site of lesion and degree of CES impairment. In order to investigate whether lesions involving the frontal lobe are more predictive of CES impairments than lesions in other brain areas, WM performance of patients with frontal lobe lesions (group F) and lesions affecting other brain areas (group NF) were compared. The role of site of lesion on patients' speed processing performance was also investigated.

Two ANCOVAs were performed taking WM or speed processing performance as dependent variables and group as factor with two levels (F and NF). The influence of other parameters, such as age, education, severity of trauma and length of time from injury on the dependent variables was controlled by entering them as covariates in the ANCOVAs.

The ANCOVA taking WM as dependent variable showed no effect of group ($p = 0.43$) on patients' performance: patients with frontal lesions exhibited a similar number of errors in the WM task (group F; 12.3) comparing to patients with other site lesions (group NF; 9.8). No significant effect of age ($p = 0.65$), education ($p = 0.30$), time since injury ($p = 0.38$) or severity of trauma ($p = 0.41$) on performance was found. Similar results were obtained on speed processing scores: Group had no influence on speed processing performance ($p = 0.83$), nor did age ($p = 0.90$), education ($p = 0.30$), time since injury ($p = 0.92$) or severity of trauma ($p = 0.24$). Patients with frontal lesions were characterized by similar reaction times as patients with lesions to other brain regions (313 vs. 287 ms).

Discussion

The central focus of the present study was to investigate whether cognitive deficits after TBI can be explained by a unique impairment of the CES or by a general slowness in speed processing. According to the WM hypothesis, the CES is involved in several cognitive domains, such as WM, divided attention, executive function and LTM [20]. Thus, an impairment of the CES should cause deficits in these cognitive functions [4, 5]. In contrast, according to the speed processing hypothesis, these deficits are considered to be the consequence of a general slowing in information processing, affecting all aspects of cognitive functioning [1, 3].

The results of the present study support the WM hypothesis. First of all, it was found that, in patients with TBI, WM is the most impaired function, suggesting that a CES damage is actually the main consequence of TBI. Secondly, frequent deficits were found in other cognitive functions which are supposed to depend on the CES, i.e. divided attention, executive functions and LTM. These deficits are correlated to each other and with WM deficits, thus supporting the WM hypothesis. Furthermore, by using multiple regression analyses, it was demonstrated that WM and not speed processing performance explained patients' performance in divided attention, executive function and LTM.

This study will now describe in more details the results concerning each of the cognitive function investigated in a group of chronic TBI patients and how deficits in these functions are related to a more general impairment of the CES.

The vast majority of patients showed highly pathological results in a test assessing WM functions, i.e. an n-back task. WM is supposed to rely on three major components: the CES, which processes and manipulates the information, and two slave systems, which temporarily maintain the information [20]. The results of the present study indicate that low WM performance is due to a CES impairment and not to deficits in the slave systems. Indeed, only 17% of patients obtained pathological results in the short-term memory task, i.e. digit span, that requires the ability to passively maintain the information, whereas more than 60% of patients obtained pathological scores in the n-back task, that requires the monitoring and the continuous updating of information in working memory.

Additionally, the present study advocates, in line with previous studies [7, 8], that patients with TBI show an impairment in divided attention. Moreover, the positive correlation between divided attention and WM deficits suggests the involvement of the CES in the distribution of attentional resources among concurrent tasks. This interpretation is in line with a recent study by Park et al. [5], who found that patients with TBI were impaired relative to normal controls in performing two tasks concurrently when these tasks heavily relied on the CES, but not when the two tasks required low levels of executive demands. Otherwise, the results exclude the possibility that divided attention deficits of patients are a consequence of a speed processing slowing [1], since a multiple regression analysis showed no effect of this factor on patients' performance.

Concerning executive functions, the results showed that patients with TBI are impaired in problem-solving, as assessed by the Tower of London test [39]. Patients needed more moves relative to normal controls to match the presented configurations, meaning they have problems in selecting, organizing and monitoring goal-directed behaviours. Moreover, the results suggest that the CES might play a role in such executive processes, as the total move score correlated with WM performance. Possibly, WM processes are particularly crucial in the initial phases of goal-directed behaviour, in which the most suitable strategies to accomplish a task have to be selected among alternatives, 'mentally' checked and, if necessary, modified. The CES might represent, therefore, the 'functional substrate' of this initial selection process, being implicated in maintaining, processing and manipulating information in WM. The same correlation between WM and executive processes was found by McDowell et al. [4]. However, since these authors used reaction times measures to evaluate both the former (dual task) and the latter (Trial Making Test and Stroop Test), the obtained correlation could partly depend on a speed processing deficit. In contrast, in the present study, by using regression analysis, it was found that speed processing cannot predict the degree of impairment in executive functions.

Finally, the results showed that patients with TBI are frequently impaired in LTM, as assessed by Buschke-Fuld test [37], which evaluates several aspects of LTM functioning. The results revealed deficits affecting either acquisition (LTR) and storage (CLTR) and retrieval processes in patients compared to normal controls.

Multiple regression analyses, performed to elucidate the nature of these memory problems, showed that acquisition and delayed recall deficits were significantly predicted by WM performance, whereas storage abilities were not. It has often been hypothesized that patients with TBI present problems in learning new information due to an impairment in engaging efficacious strategies during encoding [40, 41]. The present study suggests that patients' encoding deficits are, at least in part, due to a CES impairment. This claim becomes more comprehensible if it is considered that an efficient strategy to learn the 10 words of the Buschke-Fuld Test could be to associate them on the basis of their semantic relationship, instead of repeating them according to the serial order of presentation. These associations require deep processing and manipulation of incoming information, that are supposed to be CES functions [20, 42]. Differently, it was found that the CES has not a crucial role in the progressive consolidation and storage of encoded information, which probably depends to a great extent on other brain regions, e.g. the hippocampus [43]. Moreover, as far as retrieval abilities are concerned, an interesting result is that WM performance predicts delayed recall performance. This is in accordance with recent evidence suggesting a considerable overlap in the frontal activation pattern for tasks requiring WM and episodic memory retrieval [44, 45]. Therefore, damage to these neural circuits would be likely to give rise to deficits in both these functions. From a more functional perspective, it is now widely accepted that free recall requires executive processes, such as cue-search and monitoring of retrieved information [46] and the CES might be implicated in maintaining and updating the material upon which these processes act. The 'working with memory' nature of free recall [46] is also supported by the positive correlation found between executive functions and delayed recall performance in this study.

In contrast, TBI seems not to cause a deficit in maintaining vigilance over a long period of time, since very few patients obtained pathological scores in sustained attention tasks. This result is in line with other studies [7, 47] and excludes the possibility that cognitive deficits found in patients with TBI are due to a general deficit in maintaining a sufficient level of vigilance to complete cognitive tasks. Concerning speed processing, about half of the patients presented pathological RTs to a visual target, thus confirming that a slowness in information processing can be a rather common deficit after TBI, as proposed by some authors [1, 3]. However, the lack of a correlation between speed processing and WM, divided attention, executive function and LTM impairments excludes that this deficit alone can explain deficits in other cognitive functions.

To summarize, it was found that TBI mainly causes an impairment of the CES and that this impairment, rather than a speed processing deficit,

can be the mechanism underlying deficits in WM, divided attention, executive functions and LTM. It is worth noting, however, that some of the authors who raised the possibility that cognitive deficits after TBI are linked to a general slowness factor [18], examined patients after a short time interval from injury, whereas in the present study only chronic patients, *still complaining of cognitive problems*, were investigated. Thus, although the effect of time post-injury has been controlled for in all the analyses, it might be that the results can be extended only to chronic TBI patients *with residual cognitive impairment* (see also [48]).

As a second aim of the study, the relationship between the characteristics of brain lesions and the degree of impairment in CES functions and in speed processing were investigated. Matarò et al. [24] found that patients who presented no visible lesions at CT scans were characterized by a better general neuropsychological outcome relative to patients with more severe brain injuries (mass lesions or diffuse injuries). Subsequently, it was investigated whether the severity of brain lesions was more predictive of the degree of CES or speed processing impairments. The results showed that patients with no detectable brain lesions presented similar speed processing performance relative to patients with diffuse or mass lesions. Patients with lesions of different severity seem to be better distinguishable in terms of WM performance, although only a trend emerged for patients with negative scan to make less errors in the n-back task comparing with patients with detectable lesions.

Given that a WM deficit is a common consequence of a brain lesion, it was further investigated whether differences in lesion site had a different impact on CES functioning. In contrast to extensive evidence supporting a strict link between CES functioning and frontal lobes [26–31], no difference emerged in WM performance between patients with frontal lobe lesions and patients with lesions in other brain areas. Other clinical studies failed in finding a clear relation between the site of brain lesions and executive function deficits in patients with TBI [49–51]. A possible explanation for these findings could be that CES functioning is sustained by a distributed cortical network, involving also parietal and temporal cortex, rather than by a unique frontal region [52, 53]. Therefore, any lesion altering this functional connectivity can cause impairments in its functioning, irrespective of the integrity of the frontal cortex [49]. This hypothesis is supported by recent neuroimaging findings showing altered pattern of cerebral activation in patients with TBI during working memory tasks relative to normal subjects [53–56].

However, it is worth noting that the anatomical correlates of behavioural deficits are particularly elusive in patients with TBI, in that small brain lesions and axonal shear injuries are difficult to detect with conventional TC and MRI techniques. This being the case, the lack of an involvement of frontal lesions on CES dysfunction cannot be considered a definite result and a more fine-grained investigation of the neural correlates of CES impairments in patients with TBI [57] is needed.

Acknowledgements

We are grateful to Eric van Diessen for kindly revising the English throughout the manuscript.

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