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Early prediction of long-term cognitive impairment after cardiac arrest

JÖRN PROHL,[1] SEBASTIAN BODENBURG,[2,3] AND STEPHAN JEFF RUSTENBACH[4]

[1]Department of Cognitive Rehabilitation, Neurological Rehabilitation Center Godeshöhe, Academic Teaching Hospital, University of Bonn, Bonn, Germany
[2]Neuropsychological Office, Hamburg, Germany*
[3]Department of Psychology, University of Hamburg, Hamburg, Germany
[4]Center for Internal Medicine and Dermatology, German Center of Competence in Health Services Research in Dermatology, University Clinics of Hamburg, Hamburg, Germany

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Abstract

This prospective study evaluated the prognostic value of early neurobiochemical markers, neuron-specific enolase and astroglial protein S-100B, for long-term cognitive outcome after cardiac arrest. Six months after admission of a cohort of 80 consecutive patients, 26 survivors were able to undergo a neuropsychological test battery. Survivors showed low test performances in attention, learning/memory, and executive functioning. Neuropsychological bedside screening during the first month significantly differentiated between patients with and without long-term cognitive impairment. The neurobiochemical marker S-100B at day 3 after admission was found to predict significant proportions of variance in specific cognitive domains (learning/memory and executive functioning). The results indicate that early neuropsychological assessment might help identify patients who run at risk of long-term neuropsychological dysfunction. This study also suggests that especially the protein S-100B provides valuable information on long-term cognitive outcomes. To understand the exact relationship, results have to be replicated in larger trials. (*JINS*, 2009, *15*, 344–353.)

Keywords: Hypoxic-ischemic encephalopathy, Prognoses, Neurobiochemical markers, S-100B, Neuron-specific enolase, Neuropsychological bedside screening

INTRODUCTION

Improvements in cardiopulmonary resuscitation (CPR) and intensive care medicine considerably increased the probability of survival after cardiac arrest. The current literature reports a survival-to-discharge rate up to 30% (Zandbergen, 2008), whereas previous studies reported a recovery of consciousness in maximal 15% of the patients (Saklayen et al., 1995).

However, these improvements resulted in an increasing prevalence of patients suffering from serious and often under diagnosed long-term neuropsychological impairment as a result of hypoxic–ischemic brain injury (Drysdale et al., 2000; Zingler et al., 2003). Neuropsychological outcome studies show that only 5% of these patients achieved full remission of cognitive impairment during the first month, and approximately 20–50% suffer from significant long-term deficits in their daily living (Grubb et al., 2007; Roine et al., 1993; Sauvé et al., 1996).

To plan and administer appropriate postresuscitation therapy, it is important to assess the degree of cerebral damage caused by cardiac arrest as early as possible (Haupt et al., 1997). During the past two decades of clinical research, neurobiochemical markers [especially the astroglial protein S-100B and the neuron-specific enolase (NSE)] were increasingly investigated and found to be prognostic markers of relevant predictive value (e.g., Berek et al., 1997; Müllges & Stoll, 2002; Rosén et al., 2001; Zandbergen et al., 1998, 2001). However, in most of these studies, outcome assessment was limited to an early stage in the postarrest phase and focused on the regaining of consciousness. Consequently, little is known about the prognostic value of these early neurobiochemical markers for neuropsychological long-term outcome.

*Private Practice, Mönckebergstraße 19, 20095 Hamburg, Germany
Correspondence and reprint requests to: Jörn Prohl, Department of Cognitive Rehabilitation, Neurological Rehabilitation Center Godeshöhe, Academic Teaching Hospital, University of Bonn, Waldstraße 2-10, 53117 Bonn, Germany. E-mail: joern.prohl@t-online.de

The present study therefore focused on the predictive value of early neurobiochemical markers for short-term neurological outcome (first month after admission) as well as long-term neuropsychological outcome (6 months after admission). The results on the prediction of short-term neurological outcome are published elsewhere (Prohl et al., 2007), where in sum, a multivariate assessment procedure, including a standardized clinical investigation, NSE and age at day 4 were found to be predictive of short-term prognosis. The gist of this article deals with the evaluation of the prognostic value of the early neurobiochemical markers NSE and S-100B for long-term neuropsychological outcome 6 months after admission. Using a prospective study design, we hoped to elucidate the heterogeneous course of hypoxic–ischemic encephalopathy after cardiac arrest.

METHODS

Research Participants

Eighty consecutive patients (38 female and 42 male; mean age: 63.79 ± 15.85 years) admitted to the intensive care clinic at the Hamburg-Eppendorf University Medical Center after in- or outpatient cardiac arrest between November 2002 and June 2006 were prospectively followed from the time of cardiac arrest up to 6 months after admission.

Inclusion criteria were the following:

(1) Nontraumatic, normothermic cardiac arrest due to cardiac disorders, respiratory failures, or hemodynamic or metabolic factors.

(2) A witnessed interval between collapse and the start of CPR had lasted maximal 15 min.

(3) Return of spontaneous circulation within 60 min.

(4) A Glasgow Coma Scale of 3 (Teasdale & Jennet, 1974), none of the patients were awake at the time of admission.

(5) No previous cardiac arrest, as well as known or coexisting neurological disorders or neoplasms of the APUD system [(amine precursor uptake and decarboxylation system) because elevated concentrations of biochemical markers have been described for these conditions].

(6) No history of psychiatric illness, no alcohol or drug dependency, and no psychotropic medication.

(7) No known learning disability.

The study was approved by the ethic committee of the Hamburger Ärztekammer (October 15, 2001) and conformed to institutional and federal guidelines for the protection of human subjects.

Measures and Procedures

Neurobiochemical assessment

Serum samples for NSE and S-100B measurements were taken at 8:00 AM on days 2, 3, and 4 after cardiac arrest (the day of admission was taken as day 1). The samples were analyzed by commercial immunoluminometric assays according to the manufacturer's instructions. NSE serum levels were measured by ECLIA® Roche/Hitachi Modular Analytics E170® (Roche Diagnostics GmbH, Mannheim, Germany), and protein S-100B by LIA-mat® Sangtec 100® (DiaSorin; Deutschland GmbH, Dietzenbach, Germany). The upper normal NSE concentration, defined as the 95th percentile, was 15.2 ng/ml, and the upper normal concentration of S-100B was 0.12 ng/ml.

Neuropsychological assessment

Patients underwent neuropsychological examination twice. A first testing was carried out within the first month after admission. This neuropsychological bedside screening included the Mini-Mental State Examination (MMSE; Folstein et al., 1975). To widen construct validity, the MMSE was supplemented by the following tasks: orientation/general knowledge and digit spans [both: Wechsler Memory Scale–Revised (WMS-R), German version (Härting et al., 2000)], word fluency (f words, animal names) (Cognitive Minimal Screening; Kessler et al., 1991), and picture memory (Snodgrass & Vanderwart, 1980). We also administered five instead of three words in the memory tests (car, flower, candle, house, and ball) and five pictures (tree, camel, clippers, saw, and bed) (Kessler et al., 1991). For scoring, we summed the correct responses to each item (Table 1). We named this screening procedure as Bedside Neuropsychological Test Battery (BNTB). It was performed on the general ward as soon as patients were able to understand instructions and to carry out test demands.

A more comprehensive neuropsychological examination was administered 6 months after admission and based on following tests covering following cognitive domains:

(1) Attention [computerized Test Battery for Attentional Performance (TAP), subscales: alertness, go/no go (version 1), divided attention (Zimmermann & Fimm, 1993); Trail Making Test (TMT), version A (Reitan, 1979)].

(2) Learning/memory [WMS-R, subscale: digit span forward; California Verbal Learning Test (CVLT), subscales: word span trial 1, total words trials 1–5, long delay free recall, recognition (Delis et al., 1987); Fragmentary Picture Test (FPT), subscale: trial B (Kessler et al., 1993)].

(3) Executive functions [WMS-R, subscale: digit span backward; TMT, version B; Regensburger Word Fluency Test (RWT), subscales: p words, g/r words, professions, fruits/sports (Aschenbrenner et al., 2001); Leistungsprüfsystem (engl. Performance Test System), subscale 3: reasoning (Horn, 1983; Sturm et al., 1993)].

(4) Visuospatial skills [Wechsler Adult Intelligence Scales, subscale: mosaic test (Wechsler, 1981); Benton Line Orientation Test (Benton et al., 1983); FPT, subscale: trial A].

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Table 1. Flow chart and scoring system of the BNTB

Test	Scores
Orientation/general knowledge	0–15
Verbal memory (1): three learning trials (five items)	0–15
Attention: backward spelling + backward counting	0–10
Word fluency (lexical): f words (1 min)	0–∞
Verbal memory (2): free recall trial	0–5
Language and visuoconstruction	0–9
Picture memory (1): three learning trials (five items)	0–15
Digit span: forward	0–6
Digit span: backward	0–6
Word fluency (categorical): animal names (1 min)	0–∞
Picture memory (2): free recall trial	0–5

Note. Each correct response is scored as 1. For fluency tests, no limit in responses exists.

All tests were conducted by the same neuropsychologist, who was kept blind to the patients' clinical data.

Statistical Analysis

Descriptive sample statistics were computed for sociodemographic characteristics, relevant clinical features of cardiac arrest patients, neurobiochemical markers (NSE and S-100B), and neuropsychological test scores. Results are given as mean, standard deviation (*SD*), median, and range. The presence of cognitive impairment was *a priori* defined as two or more neuropsychological test scores of 1.5 *SD* or one test score of 2 *SD* below the mean of the norm population. The neuropsychological performance on the screening instrument and on the test battery of the two groups of impaired/not impaired patients was compared with *t* tests for independent samples. To test the appropriateness of parametric testing, sensitivity analyses were conducted by Mann–Whitney *U* tests. The results of the parametric tests were replicated in each case and thus are not presented.

To evaluate the predictive value of the early neurobiochemical markers (NSE days 2–4 and S-100B days 2–4) for neuropsychological outcome, hierarchical multiple regressions were conducted. To reduce the number of dependent variables, neuropsychological test scores were *z*-transformed with the mean and *SD* of the normative population and averaged for the domains of attention, learning/memory, executive functioning, and a total score of neuropsychological performance (see Table 3 for the assignment of tests to these domains). Average *z*-scores for learning/memory were computed on the basis of the *z*-scores for WMS-R digit span (forward), CVLT trial 1–5, CVLT recognition, and FPT trial B. Because so few subjects were impaired on visuospatial tests (Table 4), we did not compute an average *z*-score for this domain.

To control for potential confounding with age, sex, and education, these variables were included in the model (first step of the hierarchical modeling) before the addition of both the neurobiochemical markers (last step of the hierarchical modeling). To gain further degrees of freedom for inference, only NSE and S-100B measurements of day 3 after admission were included in the model. Exploratory analyses showed a high correlation between the concentration at days of measurement (days 2–4) for both NSE and S-100B. To avoid this multicollinearity in regression analyses, the median day of measurement (day 3) was selected.

The BNTB was not considered for inclusion here because of an expected correlation to the standardized neuropsychological tests (both are indicators of the same construct and any other association would have been obscured by this natural correlation) and the reduction in sample size to $n = 21$ because of additional missing data. To examine the diagnostic validity of the BNTB to differentiate between cognitively impaired patients from those who were not impaired after 6 months, a receiver operating characteristic (ROC) analysis was carried out.

RESULTS

Subject Characteristics

Overall, 33 patients survived the 6 months after admission and the remaining 47 patients had a very poor neurological outcome (death or persistence vegetative state). Twenty-six patients (79% of the 33 survivors) gave "deferred consent" [consent to continue in the study when they became sentient after collection of early serologic and cognitive data (Abramson et al., 1986)]. They participated in this study until the neuropsychological assessment at 6 months. Main reasons for nonparticipation were severe disorders of attention ($n = 3$), refusing consent ($n = 3$), and cancer ($n = 1$). The subsequent results therefore rely on the remaining 26 survivors with a mean age of 61.9 (±13.2) (Table 2).

Table 2 depicts relevant sample statistics concerning sociodemographic and clinical characteristics. The sample characteristics are typical for patients admitted to an intensive care unit because of cardiac arrest as a result of heart disease. In addition, Table 2 gives the time-release patterns of NSE and S-100B. NSE peaks on day 2 and tends to

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Table 2. Description of the sample

	Total sample (N = 26)				
	n	*M*	*SD*	*Mdn*	Range
Sociodemographic					
Age, total sample (years)	26	60.65	13.78	63.00	38–91
Female	12	61.42	14.19	63.50	39–82
Male	14	60.00	13.91	62.00	38–91
Education (years)					
Up to 9	11				
10–12	10				
More than 12	5				
Cardiac arrest					
Initial rhythm (*n*)					
Asystole	6				
VF	20				
Pathogenesis (*n*)					
Cardiac	21				
Respiratory	2				
Hemodynamic	2				
Metabolic	1				
CPR location (*n*)					
In hospital	16				
Out of hospital	10				
Neurobiochemical					
NSE at day 2 (ng/ml)	26	15.03	5.10	13.00	7.10–27.70
NSE at day 3	26	11.55	4.67	10.81	4.60–27.10
NSE at day 4	26	10.53	3.56	9.75	5.00–19.20
S-100B at day 2 (ng/ml)	26	0.40	0.47	0.20	0.01–1.93
S–100B at day 3	26	0.29	0.25	0.19	0.01–0.88
S-100B at day 4	26	0.31	0.30	0.22	0.02–1.01

Note. VF, ventricular fibrillation.

decrease from days 2 to 4, whereas the protein S-100B concentration follows an U-shaped distribution. Whereas NSE drops down to the upper normal NSE concentration (<15.2 ng/ml), the serial measurement of protein S-100B concentration remains above the normal level (>0.12 ng/ml) on all days.

Table 3 shows the performance of the total sample on the BNTB (≤1 month after admission) and on the neuropsychological test battery (6 months after admission). The results are given as raw and *T*-scores, the latter for an easy way to judge the impairment relative to the performance of the norm population. With exception of two test parameters (CVLT, trial 1 and trials 1–5), test performances were observed within the norm ($40 \leq T \leq 60$). Since the BNTB included different test scales, a comparison to norms was not possible. For scoring, correct responses were counted; the observed scores ranged from 45 to 104. Moreover, the BNTB was administered only to 21 patients since 5 were not capable of testing within the first month due to an impairment in vigilance.

In addition, Table 4 gives the number of subjects with a *T*-score of less than 40. Patients were most commonly impaired on following functions: visual motor speed (TMT, version A), the ability to perform parallel information processing (TAP, divided attention), the ability to learn (CVLT, trials 1–5), memory driven flexibility (TMT, version B), and word fluency (RWT, g/r; professions) as an executive skill. The pattern of impairment mirrors the wide spectrum of cognitive dysfunctions typically observed in cardiac arrest patients.

Furthermore, this table shows the means and *SD*s of the neuropsychological performance for patients categorized as impaired/not impaired (for details see "Methods" section). *T*-tests revealed significant differences between the groups on almost all neuropsychological tests.

To evaluate the diagnostic validity of the BNTB, a ROC analysis was performed (Figure 1). The area-under-curve value of 0.88 (SE = 0.77, $p \leq .01$; lower 95% CI = 0.73, upper 95% CI = 1.03) indicates that this screening instrument differentiated significantly between survivors with and without long-term cognitive dysfunction within the first month after admission. A BNTB cutoff value of 81.5 yields a specificity of 100% and a corresponding sensitivity of 30%, whereas a cutoff value of 96.5 gives a sensitivity rate of 100% and corresponding specificity rate of 36%. The BNTB threshold value that gives the greatest combined sensitivity and specificity for cognitive impairment at 6 months is 94.5 (specificity 82% and sensitivity 90%).

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Table 3. Neuropsychological test performance of the sample (raw and *T*-scores)

	Raw scores				*T*-scores			
	M	*SD*	*Mdn*	Range	*M*	*SD*	*Mdn*	Range
Global cognitive screening								
BNTB (less than or equal to a month)[a]	90.19	12.88	94	45–104	—	—	—	—
Attention								
TAP alertness	322.24	160.71	268	196–779	43.56	10.80	46	20–60
TAP alertness/tone	300.88	127.40	264	188–723	41.88	9.68	45	20–69
TAP go/no go (version 1)	518.60	122.24	487	383–812	41.08	10.58	43	20–56
TAP divided attention	773.44	164.95	742	583–1383	41.56	11.45	44	20–64
TMT version A	60.52	45.18	49	17–224	43.24	8.59	37	36–63
Learning/memory								
WMS-R digit span (f)	7.20	1.58	8	3–10	48.88	8.23	51	28–62
CVLT trial 1	5.12	2.17	5	2–10	38.80	11.66	40	20–60
CVLT trials 1–5	42.52	13.34	43	19–68	38.04	16.77	43	5–66
CVLT LDFR	9.04	4.12	10	1–16	43.60	16.04	50	20–70
CVLT recognition	13.36	3.12	15	6–16	45.20	14.75	50	20–60
FPT trial B[a]	19.84	6.64	19	11–35	—	—	—	—
Executive function								
WMS-R digit span (b)	5.64	1.38	6	2–8	45.36	7.52	47	29–58
TMT version B	133.00	77.99	119	28–356	42.24	8.87	37	26–63
RWT p words	12.88	5.64	11	4–26	45.20	7.50	47	36–60
RWT g/r words	15.48	6.12	15	5–30	43.16	7.63	40	36–60
RWT professions	18.96	6.54	19	5–33	42.00	6.73	40	36–64
RWT fruits/sports	16.64	5.60	16	7–34	43.96	7.91	42	36–64
LPS scale 3 reasoning	19.72	6.33	20	6–34	51.44	8.12	53	38–68
Visuospatial skill								
WAIS mosaic test	22.88	8.20	22	6–39	47.40	8.53	47	24–59
BLOT	25.20	3.01	25	20–33	49.96	6.38	51	36–61
FPT trial A[a]	27.60	4.79	28	20–40	—	—	—	—

Note. BLOT, Benton Line Orientation Test; BNTB, Bedside Neuropsychological Test Battery; CVLT, California Verbal Learning Test; FPT, Fragmentary Picture Test; LDFR, Long Delay Free Recall; LPS, Leistungsprüfsystem (Performance Test System); RWT, Regensburger Word Fluency Test; TAP, Test Battery of Attentional Performance; TMT, Trail Making Test; f, forward; b, backward; WAIS, Wechsler Adult Intelligence Scales; WMS-R, Wechsler Memory Scale-Revised.
[a]T-scores were not available.

Finally, Table 5 summarizes the results of the four hierarchical multiple regressions of neuropsychological performance on the early neurobiochemical markers. The different models for the domains of attention, learning/memory, executive functioning, and total neuropsychological performance are displayed in the columns of the table. Relevant statistics for each model are given in the rows of the table, beginning with the usual omnibus test of the significance of the set of predictors for the initial regression model (includes only demographic variables) as well as for the final regression model (includes demographic variables plus neurobiochemical markers). Of particular interest are the *F*-change statistics in hierarchical regression since they show the significance of the addition of the neurobiochemical markers as predictors (i.e., NSE and S-100B) to the demographic predictors (i.e., Sex, Age, and Education) already included in the model. In the next row, the coefficient of determination (R^2) is given for the final model, both in the sample, and an adjusted estimate of the variance explained in the population. The remaining rows give the standardized regression coefficients included in the final model along with their usual tests of significance.

The regressions significantly explained about 40% of the variance in learning/memory and executive functioning *z*-scores. Due to the nonsignificant proportion of variance explained in attention scores, the regression on total neuropsychological performance is also not significant. None of the demographic variables controlled for (age, sex, education) was significantly related to the neuropsychological outcomes in both steps of all models. The addition of both early neurobiochemical markers significantly changed the model fit for learning/memory and executive functioning scores.

In both significant regressions, the only significant predictor is the concentration of the protein S-100B at day 3 after admission. The negative unstandardized regression coefficients ($b = -2.63$ for learning/memory and $b = -2.90$ for executive functioning; data not shown) indicate that an increase in S-100B by a factor of 2.6 (for learning/memory) and 2.9 (for executive functioning) is associated with a reduction of the respective neuropsychological performance by 1 *SD*.

A significant negative regression coefficient of comparable size was also found in the regression on the total scores of neuropsychological performance, but the omnibus test failed to reach significance.

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Table 4. Neuropsychological performance by cognitive impairment group

	Test performance (*T*-score <40), *n*	Cognitive sequelae (*n* = 15)		No cognitive sequelae (*n* = 11)		
		M	*SD*	*M*	*SD*	*t* Test
Global cognitive screening						
BNTB (less than or equal to a month)	—	83.00	14.61	96.73	6.40	2.84*
Attention						
TAP alertness	5	38.07	11.00	50.55	5.18	3.46**
TAP alertness/tone	6	37.64	10.25	47.27	5.57	2.80**
TAP go/no go (version 1)	9	37.93	12.46	45.09	5.94	1.75
TAP divided attention	10	39.00	14.01	44.82	6.21	1.28
TMT version A	13	38.07	3.73	49.82	8.61	3.58**
Learning/memory						
WMS-R digit span (f)	1	44.07	6.80	55.00	5.39	4.57***
CVLT trial 1	9	35.00	11.60	43.64	10.27	1.90
CVLT trials 1–5	10	28.50	15.52	50.18	8.49	4.07***
CVLT LDFR	8	33.57	13.36	56.36	8.09	4.71***
CVLT recognition	5	37.86	15.28	54.55	6.88	3.45**
FPT trial B[a]	8	22.20	5.82	17.09	6.67	2.08*
Executive function						
WMS-R digit span (b)	8	40.79	6.31	51.18	4.17	4.95***
TMT version B	14	37.36	3.79	48.45	9.71	3.25**
RWT p words	8	40.50	4.26	51.18	6.42	5.25***
RWT g/r words	10	39.21	4.23	48.18	8.18	3.59***
RWT professions	13	39.00	4.17	45.82	7.59	3.04**
RWT fruits/sports	8	40.50	5.61	48.36	8.44	2.86**
LPS scale 3 reasoning	2	47.07	7.24	57.00	5.42	3.99***
Visuospatial skill						
WAIS mosaic test	4	42.36	7.62	53.82	4.26	4.45***
BLOT	1	47.57	6.00	53.00	5.73	2.26*
FPT trial A[a]	1	29.13	4.49	25.82	4.58	1.85

*$p \leq .05$.
**$p \leq .01$.
***$p \leq .001$.
Note. See Table 3 for key to abbreviations.
[a]Since *T*-scores were not available, mean test values and *SD* are given. (FPT values in column 2 present number of subjects who score 2 *SD* below the mean of an age-adjusted control group.)

To demonstrate that the association between neuropsychological performance and S-100B is not a methodological artifact, Figure 2a and 2b show the histograms of the residuals for the learning/memory and executive functioning models, and Figure 3a and 3b show the partial regression plots of S-100B with the cognitive variables, respectively.

While the distribution of the residuals is far from perfect, they are acceptable in a model with 25 degrees of freedom. The only obvious deviation from normality is a single outlier with a negative residuum apparent in both graphs. As can be seen from the partial regression plots (Fig. 3a and 3b), these cases are not very influential and thus were not excluded from the model.

The scatter plots in Figure 3a and 3b show the partial correlations between S-100B and neuropsychological *z*-scores of learning/memory and executive functioning *z*-scores graphically. Both graphs indicate clearly that neuropsychological performance decreases linearly with an increase in S-100B. The outlier does not disturb this relation or the interpretation.

DISCUSSION

This prospective study related early neurobiochemical markers to long-term neuropsychological outcome to shed light on the heterogeneous course of hypoxic–ischemic encephalopathy after cardiac arrest. Before turning to the key result of this study, let us focus on two other findings.

First, low test performances were found in the domains of attention, learning/memory, and executive functioning. The range of cognitive impairments observed reflects the neuropathological outcome of global cerebral hypoxia very well and is in accordance with results of previous studies (Caine & Watson, 2000).

Furthermore, the neuropsychological bedside screening (BNTB) applied in the first month after admission differentiated significantly between patients with and without long-term cognitive impairment. It is important to point out that none of these patients received systematic neuropsychological rehabilitation. This result is a strong argument for

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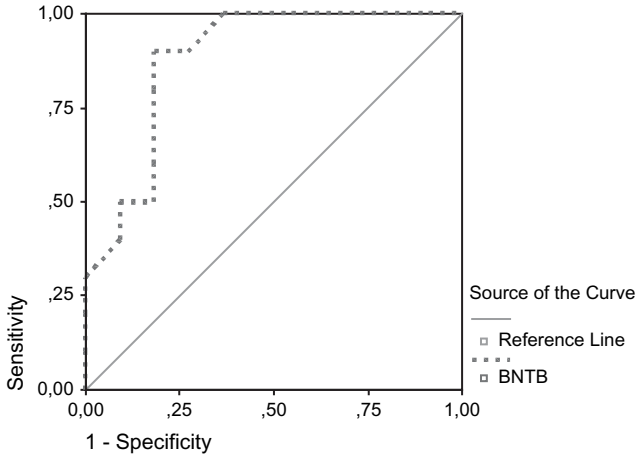

Fig. 1. ROC curve of BNTB to distinguish subjects cognitively impaired at 6 months from those who are not impaired.

neuropsychological testing as early as possible, even in intensive or cardiac care units. An early neuropsychological bedside screening would further assist physicians in planning postresuscitative rehabilitation programs and in the formulation of realistic goals of rehabilitation. The survivors themselves would benefit from early bedside screening of cognitive functioning even in later everyday life. In addition, the results of early bedside testing should be communicated to relatives in order to guide their expectations, duties, and responsibilities in daily living after discharge of the patients (Sunnerhagen et al., 1996).

While neuropsychological bedside screening is increasingly used in clinical settings to detect and to quantify the severity of cognitive impairment early, it is not probable that these screenings will be sufficient for the detection of different types of cognitive impairment (Nelson et al., 1986). This limitation holds for the bedside instrument used in this study, too, but it was possible to differentiate between patients with and without long-term cognitive impairment within 1 month after admission. In addition, the screening procedure was applicable even for patients in postcomatose conditions.

Finally, the present study revealed a significant relationship between the early biochemical marker S-100B measured on day 3 after admission and neuropsychological outcomes in the domains of learning/memory and executive functioning 6 months later. Thus, early concentrations of S-100B seem to be related to subtle long-term cognitive dysfunctions.

These data corroborate the study results involving other patient populations [e.g., stroke, traumatic brain injury (TBI)], where the protein S-100B was found to be significantly related to long-term neuropsychological outcomes (Herrmann et al., 2001; Wunderlich et al., 1999). Recently, Grubb et al. (2007) found that S-100B concentration, measured shortly after out-of-hospital cardiac arrest, is a useful predictor to identify patients at risk of cognitive impairments at discharge. They found a moderate negative relationship between S-100B levels and the memory test scores of the Rivermead Behavioral Memory Test.

Serum S-100B may just be a marker of glial injury (Laming, 1998; Zimmer et al., 1995). However, there is some evidence that overexpression of S-100B may induce cellular apoptosis or necrosis, thereby contributing to brain damage, but also that deregulated expression of S-100B may contribute positively to cellular reorganization following injury (Herrmann et al., 2003; Van Eldik & Wainwright, 2003). For example, Kleindienst et al. (2005) found evidence that an endogenous repair mechanism exists for cognitive dysfunction following experimental TBI. After intraventricular S-100B infusion, they found neurogenesis in the adult rat hippocampus, which adumbrates the neurotrophic potential of this protein. The balance between the detrimental and the beneficial effects of S-100B may depend on the concentration and the time elapsed after brain injury, among other factors (Van Eldik & Wainwright, 2003).

With regard to this study, the nonsignificance of the regression on overall neuropsychological outcome seems to be due to the relatively small association of S-100B concentration to attentional performance on the one hand and to statistical power on the other hand—given a sample size of $N = 26$. This leads directly to the limitation of this study

Table 5. Results of the hierarchical regression models of neuropsychological outcome on early neurobiochemical markers

	Attention		Learning/memory		Executive function		Total	
ANOVA								
$F_{\text{Initial Model}}(df1, df2)$	1.265 (3,22), $p \leq .311$		1.501 (3,22), $p \leq .242$		1.837 (3,22), $p \leq .170$		1.547 (3,22), $p \leq .231$	
$F_{\text{Final Model}}(df1, df2)$	1.350 (5,20), $p \leq .285$		2.726 (5,20), $p \leq .049$		2.900 (5,20), $p \leq .040$		2.030 (5,20), $p \leq .118$	
$F_{\text{Change}}(df1, df2)$	1.407 (2,20), $p \leq .268$		3.957 (2,20), $p \leq .036$		3.800 (2,20), $p \leq .040$		2.450 (2,20), $p \leq .112$	
$R^2_{\text{Final Model}}$	.252		.405		.420		.337	
Adjusted $R^2_{\text{Final Model}}$	.065		.257		.276		.171	
$R^2_{\text{Change (Initial to Final Models)}}$	.105		.235		.220		.163	
$\text{Coefficients}_{\text{(Final Model)}}$	$\beta(t)$	$p \leq$	$\beta(t)$	$p \leq$	$\beta(t)$	$p \leq$	$\beta(t)$	$p \leq$
Sex	.187 (−0.91)	.376	.133 (0.72)	.478	.086 (0.47)	.643	.156 (0.80)	.432
Age	−.220 (−1.07)	.297	−.323 (−1.77)	.092	−.275 (−1.52)	.144	−.270 (−1.40)	.177
Education	.008 (−0.04)	.968	−.063 (−0.34)	.739	.159 (0.89)	.395	.031 (0.16)	.877
NSE	.216 (−0.96)	.351	.005 (0.02)	.982	.094 (0.47)	.643	.142 (0.67)	.513
S-100B	−.369 (−1.67)	.111	−.493 (−2.50)	.021	−.510 (−2.62)	.016	−.454 (−2.19)	.042

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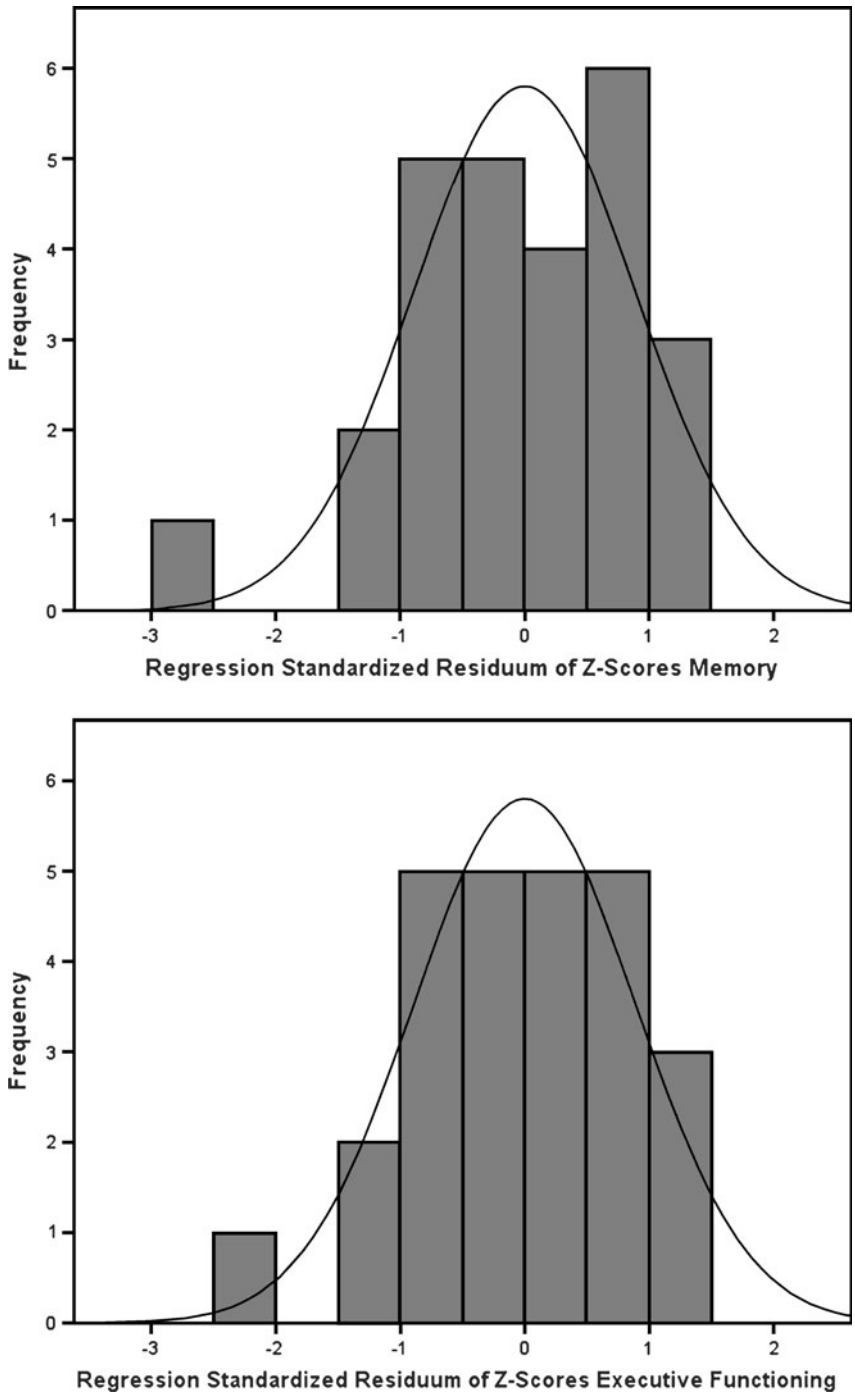

Fig. 2. Histograms of the standardized residuums in the regression models of (a) learning/memory *z*-scores and (b) *z*-scores of executive functioning.

presented: the results need to be interpreted very cautiously for several reasons.

First of all, this study only included patients capable of comprehensive neuropsychological examination, which is just a subgroup of cardiac arrest survivors. Second, the sample is very heterogeneous with respect to cardiac arrest characteristics (Table 2). Third, the generalizability of the results is restricted by all the limitations mentioned above.

Nevertheless, when considering the relatively sparse number of longitudinal studies on the outcome of cardiac arrest survivors, the results presented are clinically relevant and worth of replication. The observed associations between S-100B concentration (measured on day 3) and long-term cognitive outcome give rise to some hypotheses about time-associated and location-related pathophysiological cascades following cardiac arrest. Yet, further studies and larger

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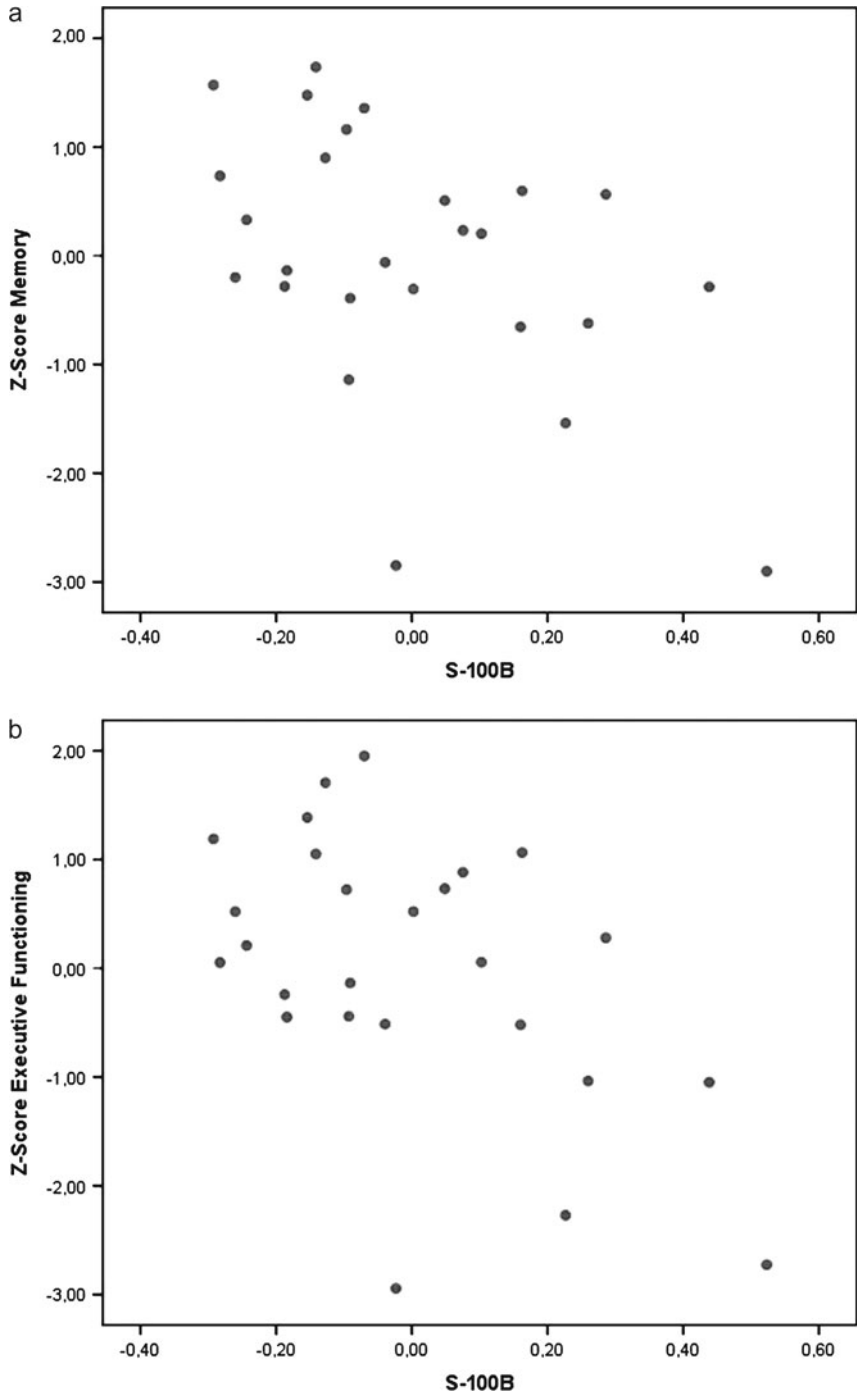

Fig. 3. Partial regression plots of S-100B in the regression models of (a) learning/memory *z*-scores and (b) *z*-scores of executive functioning.

sample sizes are needed to understand the underlying pathophysiology of adverse outcomes in such patient populations. The results presented give first hints for the further exploration of these mechanisms.

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