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Early Computed Tomography Frontal Abnormalities Predict Long-Term Neurobehavioral Problems But Not Affective Problems after Moderate to Severe Traumatic Brain Injury

Jacoba M. Spikman,^{1,2} Marieke E. Timmerman,³ Annemiek Coers,² and Joukje van der Naalt²

Abstract

Behavioral problems are serious consequences of moderate to severe traumatic brain injury (TBI) and have a negative impact on outcome. There may be two types: neurobehavioral problems, manifesting as inadequate social behavior resulting from prefrontal system damage, and affective behavioral problems, resulting from emotional distress as a reaction to the brain injury. In the present study we investigated whether these two types of behavioral problems, as indicated by proxies, could be distinguished in a group of chronic TBI patients and whether early indicators of prefrontal damage on imaging could predict long-term neurobehavioral problems. Computed tomography (CT) imaging data on admission were used to identify frontal lesions. Three hundred twenty-three moderate to severe TBI survivors received 2 to 16 years post-trauma an aftercare survey with seven questions asking for changes in behavior and affect, presented both to patients and their proxies. One hundred eighty-six patients (59%) answered the behavioral questions; 42% had frontal lesions on CT. Ordinal common factor analysis on proxy scores yielded two factors, with behavior and affective items clearly separated and the anger item mediocre related to both factors. Three scales were created: Behavior, Affective and Anger. Frontal patients scored significantly higher on the Behavior and Anger scales. Logistic regression analysis showed a fourfold increase of long-term neurobehavioral problems in patients with frontal lesions. Long-term neurobehavioral problems were significantly correlated to one-year outcome and return to work in the long term. We conclude that in patients with moderate to severe TBI neurobehavioral and affective problems can be distinguished. Early CT frontal abnormalities predict long-term neurobehavioral problems, but not affective problems.

Key words: affective problems; CT; frontal abnormalities; neurobehavioral problems; traumatic brain injury (TBI)

Introduction

TRAUMATIC BRAIN INJURY (TBI) is a major, worldwide health problem. TBI survivors, in particular those with moderate to severe injuries, often encounter long-term cognitive, emotional, and behavioral problems, which affect daily life functioning, community integration, and quality of life negatively.^{1–3} In particular, behavioral sequelae are considered as serious and persistent consequences, which are even more strongly associated with problems in daily life and an unfavorable social outcome than cognitive deficits.^{4–6} Several studies found that behavioral problems frequently occur after TBI. For instance, frequencies of behavioral disturbances in patients with severe TBI were reported to be about 75%.^{7,8} Benedictus and associates³ investigated outcome in the chronic stage in a group of 434 adults with mild to very severe TBI; 55% encountered behavioral problems. Frequencies increased with higher injury severity, but even 33% of the patients with mild TBI had behavioral problems.

However, the term *behavioral problems* may represent different syndromes. There is reason to believe that neurobehavioral problems with respect to inadequate social functioning can be dissociated from affective problems, that is, depression or anxiety. Warriner and colleagues⁹ examined a group of 300 TBI patients with the Minnesota Multiphasic Personality Inventory (MMPI) and identified dissociable subtypes of affective versus neurobehavioral sequelae. Unfortunately, injury-related data were inconsistently available, and consequently, could not be related to the presence of the different subtypes. Several other studies investigated behavioral sequelae after TBI from a neuropsychiatric perspective and found evidence for a distinction between sequelae that could be qualified as *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) Axis I (affective) disorders and those that were more in accordance with AXIS II (personality) disorders.^{10–13}

Neurobehavioral changes after TBI refer to those changes in social and interpersonal skills that are labeled by significant others as personality changes and that manifest as inappropriate and

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disinhibited social behavior.^{3,9,14,15} Labels frequently used to describe these behaviors are anger and aggression, emotional indifference and disinterest in others, childishness, and apathy.^{2,6,16,17}

These aforementioned neurobehavioral changes are associated with damage to prefrontal areas, which are particularly vulnerable in TBI.^{18,19} Especially in patients with moderate to severe TBI both focal as well as diffuse axonal damage has been demonstrated in these areas.²⁰ Hence, there is reason to assume that prefrontal damage constitutes a risk factor for developing neurobehavioral problems.

Because neurobehavioral changes are often accompanied by impaired self-awareness,^{21,22} TBI patients tend to underreport behavioral difficulties in comparison with physical²³ or cognitive problems.²¹ This implies that for patients, as well as for their relatives, awareness of the extent, nature, and impact of neurobehavioral changes may develop slowly over time. In a recent study Ponsford and coworkers²⁴ compared complaints of TBI patients at 2, 5, and 10 years post-injury and found that there was an increase over time in reported inappropriate social behavior, in particular for patients with severe TBI. It seems likely that this was not due to an increase of the problems themselves, but to a gradually augmented awareness over time. An alternative explanation might be that TBI accelerates neurodegenerative processes resulting in the emergence of behavioral problems years after the injury. Anyhow, not being able to recognize or acknowledge neurobehavioral problems in early stages of recovery will hamper timely intervention to prevent a negative outcome.³ Hence, it is important to find early indicators of a risk for developing social neurobehavioral deficits. A powerful indicator might be the presence of frontal damage on neuroimaging. There is general agreement that magnetic resonance imaging (MRI) measures are more sensitive methods to detect such damage than computed tomography (CT).^{25,26} However, MRI is more expensive and can only be performed in a later stage, which implies that many patients never get a MRI scan. For patients in the acute phase of TBI, CT is the most relevant imaging procedure for the detection of lesions; it can be immediately, rapidly, and easily performed, even in agitated patients.²⁷ Consequently, CT data will be far more widely available than MRI data.

For that reason we investigated the predictive value of early CT for long-term neurobehavioral changes, as rated by significant others, in a population of moderate to severe TBI patients. A related question is whether neurobehavioral changes can be distinguished from affective changes. We expect neurobehavioral changes to be related to frontal damage on CT, but affective changes not. In addition, we looked at self-awareness of patients by comparing patient with proxy ratings. Finally, we investigated the extent to which neurobehavioral and affective changes were related to outcome determined at one year post-injury and return to work in the long term.

Methods

Participants and procedure

All adult patients with moderate or severe TBI who had been admitted between 1996 and 2010 to the University Medical Centre Groningen, a level one trauma center, and had survived the trauma were eligible for this study. Trauma data of these patients were stored in an anonymized database. Based on the Glasgow Coma Scale score (GCS) on admission the patient group comprised moderate (GCS 9–12) and severe injuries (GCS 3–8).

Non-contrast CT was performed directly after admission to the Emergency Department as part of routine TBI examination. Images were reviewed by an experienced neuroradiologist. For CT classification the Marshall score²⁸ was used comprising six categories:

(1) no abnormalities; (2) diffuse injury, lesions <25 cc and midline shift <5 mm; (3) diffuse injury lesions <25 cc, compressed or absent basal cisterns; (4) diffuse injury, lesions <25 cc, midline shift >5 mm; (5) any lesion surgically evacuated; and (6) lesions >25 cc, not surgically evacuated. In addition, intracranial abnormalities were coded as lesions on CT if a hemorrhagic lesion with or without surrounding edema was present. Regional location of lesions was coded as frontal, temporal, occipital, parietal, and brainstem/cerebellum. Outcome was determined with the extended Glasgow Outcome Scale (GOSE²⁹) as well as with the Differential Outcome Scale (DOS³) by an experienced neurologist (JvdN) one year after injury. The GOSE comprises eight outcome categories: (8) good recovery; (7) good recovery with minor deficits; (6) moderate disability, return to previous work with some adjustments; (5) moderate disability, work at lower level of performance; (4) severe disability, activities of daily living (ADL)-independent; (3) severe disability, complete ADL-dependent; (2) vegetative state; and (1) death. The DOS comprises four scales: Physical, Cognitive, Behavior, and Social, each of which can yield a maximum of 5 points. Total DOS scores range from 4 to 20. For the present study, the total DOS score and all subscales except Social were used. This latter scale measures mainly Return to Work,³ and therefore would overlap with our long-term Return to Work measure.

In total, 558 patients were admitted with moderate or severe TBI. Exclusion criteria comprised mortality during hospital admission (110), age younger than 14 years at the moment of impact and age younger than 18 during the investigation period (108), and vegetative state or severe impairment (precluding to filling out the questionnaire) (11), leaving 329 patients to include. All remaining patients of whom the address could be traced received an aftercare survey in the period between 2009 and 2012 ($n=323$). This was sent and returned (if patients consented and filled out the survey) by regular mail. If a patient did not respond, no further actions were undertaken. Questionnaire data were collected in compliance with the ethical regulations of our institution, and after anonymization were added to the database.

Measures

The aftercare survey comprised questions concerning patient's aftercare, personal situation, and outcome. This included seven questions that asked for changes in behavior and affect, to the patient as well as to a proxy. The latter was with the purpose of obtaining a more objective view on the patient's problems in case patients had limited self-awareness.

The behavioral questions were chosen on the basis of frequently mentioned changes in the literature and were the following for the patients:

1. Do you get angry more often since you sustained a TBI? (Anger)
2. Are you emotionally indifferent since you sustained a TBI? (Indifferent)
3. Do you behave more childish since you sustained a TBI? (Childish)
4. Do you have less initiative since you sustained a TBI? (Apathy)

The affective questions were the following for the patients:

1. Do you feel sad more often since you sustained a TBI? (Sad)
2. Do you feel depressed more often since you sustained a TBI? (Depressed)
3. Do you feel anxious more often since you sustained a TBI? (Anxious)

In the questions to the proxy, the questions were posed in terms of "the patient." All questions could be answered with "Yes" or "No."

Further, it was asked whether patients had been able to return to work fully, yielding a dichotomous variable: Return to Work (RTW) with score 0) Complete return to work and 1) Incomplete return to work.

Statistical analysis

To determine whether these questions could be divided according to the presumed underlying behavioral and affective domains, an exploratory ordinal common factor analysis was performed on the binary (proxy) data. A polychoric parallel analysis with 95% boundary was used to indicate the number of factors, with unweighted least squares as the method of extraction, and Promin as rotation. All analyses were performed with the software program FACTOR.³⁰ The criteria for linking questions to a particular factor were that the loading in absolute value was >0.3 and that the factor was interpretable. For the scale(s) thus established we computed scale scores. Similar scales were created for the patient self-ratings.

All other analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22.0 (SPSS Inc., Chicago, IL). Differences between the (sub)groups were analyzed by means of χ^2 (in case of ordinal variables), *t* tests, or Mann-Whitney U tests (in case of non-normal distribution of the data). Differences between self and proxy scores for the scales were calculated by means of paired samples *t* tests. To analyze associations between the self and proxy scales, and between the scales with outcome measures and return to work, Spearman correlations were calculated.

Additional logistic regression analyses were performed on the proxy scales for which differences were found, to analyze the following predictors: presence of frontal lesions (Frontal: 1; Non-frontal: 0), severity of injury (Severe GCS 3–8: 1; Moderate GCS 9–12: 0), age (50 years and older: 1; 14–50: 0), and sex (Male: 1; Female: 0). If necessary, scale scores were dichotomized into: No changes: 0; At least one change in the domain: 1.

Results

Table 1 summarizes the characteristics of the patient group. Of the 323 patients who received the questionnaire, 59% responded. *T* tests did not show significant differences between responders and nonresponders for age ($t = -0.22$, $p = 0.82$), GCS score ($t = -0.21$, $p = 0.83$), GOSE ($t = -1.71$, $p = 0.09$), or DOS ($t = -1.8$, $p = 0.07$). χ^2 tests showed no differences between both subgroups with regard to mechanism of injury ($\chi^2 = 1.2$, $p = 0.94$) but showed a significantly higher percentage of males in the group nonresponders ($\chi^2 = 5.8$, $p = 0.02$). Within the group of 190 responders, for 4 patients either proxy scores were missing or patient scores and therefore these were excluded from the further analyses. Of the remaining group of 186 patients 42% had frontal lesions on CT. This did not differ significantly from the percentage of frontal lesions in the nonresponder group (42%; $\chi^2 = 0$, $p = 1.0$). *T* tests or χ^2 tests revealed no significant differences between the frontal and nonfrontal groups in the responder group for age ($t = 0.40$, $p = 0.69$), GSC score ($t = -0.10$, $p = 0.92$), time since injury ($t = 1.04$, $p = 0.30$), sex ($\chi^2 = 3.8$, $p = 0.057$), or mechanism of injury ($\chi^2 = 5.8$, $p = 0.35$). However, *t* tests showed differences with regard to one year outcome scores, with patients in the nonfrontal group having slightly better outcome scores; GOSE ($t = 2.2$, $p = 0.029$), DOS ($t = 2.5$, $p = 0.014$).

Behavioral and affective questions

Table 2 shows percentages of patients and proxies answering “Yes” per question. Overall, the highest score of both was on Anger. For the behavioral questions, percentages of proxies answering “Yes” were clearly higher than those of patients; for the affective questions, percentages of patients and proxies were

TABLE 1. CHARACTERISTICS OF THE PATIENT GROUP

	Nonresponders N = 133	Responders N = 190	Included responders: Frontal N = 78	Included responders: Nonfrontal N = 108
% Male	81	68	76	62
Age at trauma				
M (SD), range	33.8 (17.7), 14–81	34.2 (16.6), 14–81	33.7 (17.1), 16–81	34.7 (16.4), 14–71
GCS score				
M (SD), range	7.4 (2.4), 3–12	7.4 (2.5), 3–12	7.4 (2.5), 3–12	7.4 (2.6), 3–12
Time since injury (years)				
M (SD), range	7.5 (3.5), 2–13	8.0 (3.7), 2–16	7.7 (3.6), 2–15	8.3 (3.7), 2–16
Mechanism of injury % (traffic accident/fall/assault/other)	(60/32/2/6)	(59/33/1/7)	(61/31/0/8)	(58/35/1/6)
GOSE				
M (SE), range	5.5 (1.5), 2–8	5.8 (1.3), 3–8	5.5 (1.3), 3–8	5.9 (1.2), 3–8
Favorable outcome ^a	70%	81%	74%	61%
Marshall score on CT (frequency)				
No abnormalities	1	4	0	6
Diffuse injury grade 2	61	54	59	51
Diffuse injury grade 3	26	25	23	27
Diffuse injury grade 4	1	5	4	6
Lesions, operated	8	10	10	10
Lesions, nonoperated	3	2	4	0
DOS				
M (SD), range	15.8 (3.3), 4–20	16.4 (2.6), 8–20	15.9 (2.8), 8–20	16.8 (2.4), 11–20

^aDefined as percentage of patients with outcome moderate disability or good outcome (GOSE >4).

CT, computed tomography; DOS, Differential Outcome Scale; GOSE, extended Glasgow Outcome Scale; M, mean; SD, standard deviation.

TABLE 2. PERCENTAGES OF PATIENTS AND PROXIES ANSWERING "YES" AND SPEARMAN CORRELATIONS

Variables	% Patients "Yes"	% Proxy "Yes"	Correlation patient-proxy
Anger	47	60	0.64***
Apathy	42	48	0.75***
Indifferent	40	47	0.53***
Childish	17	35	0.55***
Sad	39	36	0.64***
Depressed	34	37	0.57***
Anxious	26	27	0.68***

*** $p < 0.005$.

comparable. The correlations between patients and proxy ratings were all moderate to high, with the highest agreement for Apathy.

Exploratory factor analysis

Parallel analysis of the proxy data indicated two factors. Table 3 shows communality values ranging from 0.46 to 0.89, indicating that the factors cover the items modestly to highly. The oblique Promin rotation yielded interpretable rotated loadings (see Table 3), and a moderate correlation of 0.55 between the factors.

Factor 1 was labeled the Affective factor, with high loadings on Sad, Depressed, and Anxious (>0.7). Factor 2 was labeled the Behavioral factor, with moderate to high loadings on Apathy, Indifferent, and Childish (>0.5). The Anger question loaded equally and modestly on both factors, which justified taking Anger into account as a separate construct. Therefore, we created three scales: Anger (one item), Behavior (three items) and Affect (three items), for the patients and proxies separately (i.e., Behavior-patient, Behavior-proxy, Affect-patient, Affect-proxy, Anger-patient, Anger-proxy).

Spearman correlations between the scales were calculated and all turned out to be significant, but moderate: Anger-patient with Behavior-patient ($\rho = 0.32$, $p < 0.005$) and Affect-patient ($\rho = 0.46$, $p < 0.005$); Behavior-patient with Affect-patient ($\rho = 0.35$, $p < 0.005$). Similarly, significant but moderate correlations were found for the proxy measures: Anger-proxy with Behavior-proxy ($\rho = 0.42$, $p < 0.005$) and Affect-proxy ($\rho = 0.42$, $p < 0.005$); Behavior-proxy with Affect-proxy ($\rho = 0.37$, $p < 0.005$).

Self and proxy scores

A paired samples t test showed a significant difference between the Behavior-patient score (mean [M] = 1.0, standard deviation [SD] = 1.0) and the Behavior-proxy score ($M = 1.3$, $SD = 1.1$; $t = -4.8$, $p = 0.000$), but no significant difference between the Affect-

patient score ($M = 1.0$, $SD = 1.1$) and the Affect-proxy score ($M = 1.0$, $SD = 1.1$; $t = -0.37$, $p = 0.71$). A χ^2 test showed a significant difference ($\chi^2 = 75.4$, $p = 0.000$) between Anger-patient and Anger-proxy, with a higher frequency for the latter.

Differences between the frontal and nonfrontal group

Percentages of patients with at least one problem on a scale were for the frontal group: Affect-proxy 54%, Affect-patient 57%, Behavior-proxy 86%, Behavior-patient 75% and for the nonfrontal group: Affect-proxy 54%, Affect-patient 55%, Behavior-proxy 63%, and Behavior-patient 48%.

Mann-Whitney U tests on the scales revealed no significant differences between both groups for both versions of the Affect scale (Affect-patient, $Z = -0.78$, $p = 0.44$) (Affect-proxy, $Z = -0.67$, $p = 0.50$). However, self- and proxy-rated behavioral problems were found significantly more in the group with frontal CT abnormalities (Behavior-proxy, $Z = -3.9$, $p < 0.005$; Behavior-patient, $Z = -3.6$, $p < 0.005$).

Anger-proxy ratings were significantly different for the frontal group (77%) and the nonfrontal group (48%; $\chi^2 = 15.2$, $p < 0.005$), Anger-patient ratings were also significantly different for the frontal group (65%) and the nonfrontal group (35%; $\chi^2 = 16.5$, $p < 0.005$).

Prediction of Behavior-proxy and Anger-proxy

A logistic regression analysis with as dependent variable the dichotomized Behavior-proxy score showed that this could be significantly predicted by a model including presence of frontal lesions, GCS score, Age, and Sex ($\chi^2 = 19.9$, $p = 0.001$, Nagelkerke R Square = 0.149). With this model, 73% of the patients could be correctly classified. In this model only the presence of frontal lesions on CT (odds ratio [OR] = 4.00, 95% confidence interval [CI] = 1.83–8.73, $p = .001$) and GCS score (OR = 2.7, 95% CI = 1.22–5.94, $p = 0.014$) were significant though modest predictors, indicating that both severity (severe TBI gave a more than 2 times higher chance than moderate TBI) and presence of frontal lesions on CT (frontal lesions gave a 4 times higher chance than no frontal lesions) predict the presence of neurobehavioral problems as rated by significant others.

A second logistic regression analysis with as dependent variable the Anger-proxy score showed that this could be significantly predicted by a model including the same set variables (Front, GCS, Age, and Sex: $\chi^2 = 17.3$, $p = 0.002$, Nagelkerke R Square = 0.122). With this model 60% of the patients could be correctly classified. In this model the presence of frontal lesions on CT was the only significant predictor (OR = 3.56, 95% CI = 1.83–6.89, $p < 0.005$).

Relation with outcome at one year and return to work

Table 4 shows the Spearman correlations of the self and proxy scales and the presence of frontal lesions with GOSE, DOS, DOS subscales Physical, Cognitive, Behavioral, and Return to Work. The Behavior-proxy scale showed of all measures the highest correlations with GOSE ($\rho = -0.36$) and DOS ($\rho = -0.43$) indicating that higher ratings of neurobehavioral problems by a proxy at on average 8 years post-injury were significantly and substantially correlated to worse outcome scores determined one year post-injury. All other scales showed also significant but more moderate correlations with the outcome measures (ranging from -0.21 to -0.25). We also looked at the DOS subscales and found low correlations with the DOS Physical subscale, moderate significant

TABLE 3. PROMIN ROTATED FACTOR LOADINGS

Variables (communality)	Factor 1 (eigenvalue 3.68)	Factor 2 (eigenvalue 1.17)
Anger (0.81)	0.47	0.38
Sad (0.87)	0.76	-0.06
Depressed (0.89)	0.83	0.11
Anxious (0.82)	0.90	-0.06
Apathy (0.67)	0.13	0.54
Indifferent (0.46)	0.06	0.57
Childish (0.57)	-0.12	0.85

Factor loadings >0.3 in absolute value are printed in bold typeface.

TABLE 4. TWO-TAILED SPEARMAN CORRELATIONS OF THE PATIENT AND PROXY VERSIONS OF THE BEHAVIOR, ANGER, AND AFFECT SCALES AND FRONTAL LESIONS WITH OUTCOME MEASURES AND RETURN TO WORK

<i>Spearman correlations</i>	<i>GOSE</i>	<i>DOS-Total</i>	<i>DOS-Physical</i>	<i>DOS-Cognitive</i>	<i>DOS-Behavioral</i>	<i>RTW</i>
Behavior-patient	-0.22**	-0.25**	-0.08	-0.21**	-0.29**	0.34**
Behavior-proxy	-0.36**	-0.43**	-0.21**	-0.35**	-0.46**	0.41**
Anger-patient	-0.23**	-0.22**	-0.11	-0.16*	-0.19**	0.24**
Anger-proxy	-0.21**	-0.23**	-0.06	-0.17*	-0.32**	0.26**
Affect-patient	-0.26**	-0.24**	-0.06	-0.24**	-0.11	0.41**
Affect-proxy	-0.24**	-0.24**	-0.03	-0.25**	-0.19*	0.40**
FRONT	-0.16*	-0.17*	-0.11	-0.08	-0.26**	-0.07

*Correlation is significant at 0.05 level; **correlation is significant at 0.01 level. Significant correlations are in bold.

DOS, Differential Outcome Scale; FRONT, Frontal lesions on computed tomography; GOSE, extended Glasgow Outcome Scale; RTW, Return to Work.

correlations with the DOS Cognitive subscale (with the highest correlation for the Behavior-proxy scale: $\rho = -0.35$ and the lowest correlations with the Anger-patient and Anger-proxy scale) and a high correlation of the Behavior-proxy scale with the DOS Behavioral subscale. Lower, but significant correlations with this DOS subscale were found for the other scales, except the Affect-patient scale which was not significant. With regard to Return to Work, determined on average 8 years post-injury, all scales showed significant correlations, with the highest for Behavior-proxy, Affect-patient, and Affect-proxy. The presence of frontal lesions showed only a substantial correlation with the DOS Behavioral subscale and was further significantly though very moderately correlated to the GOSE and DOS only.

Discussion

This is the first study to demonstrate that frontal abnormalities on acute-stage CT in patients with moderate to severe TBI are associated with long-term neurobehavioral changes but not with affective changes. This is very relevant, because neurobehavioral changes are known to have adverse consequences for the daily life functioning of patients. Hence, they should be assessed as early as possible to enable timely treatment or preventive counseling. In fact, we found that patients with frontal CT abnormalities have a 4 times higher chance on having neurobehavioral problems many years after trauma than patients without frontal abnormalities, in addition to the more than 2 times higher chance when the TBI had been severe. Although the variance explained by these models was modest, this still justifies the conclusion that knowledge of frontal integrity based on CT results significantly increases the precision of predicting who are at risk for neurobehavioral problems.

Behavioral changes are common after moderate to severe TBI.^{3-5,24} We found that in a substantial part of our patient group behavioral problems were present several years post-injury, but also that percentages of problems varied considerably across the different problem categories. This illustrates that behavioral changes are not a single-domain entity. Several authors describing behavioral changes after TBI label these either as neurobehavioral sequelae, encompassing personality changes, including agitation and aggression, or as affective sequelae, including depression and anxiety.^{9,10,13} A main question was therefore whether these two categories of changes could be distinguished. For that reason, we presented patients questions based on terms used in the literature to describe the different features covered by each category. Ordinal factor analysis on the chosen items yielded indeed two distinctive factors that could clearly be labeled as a neurobehavioral and an

affective factor. Moreover, the correlation between both factors was moderate, indicating that they represent different domains of behavioral changes. Prigatano³¹ has already argued that the behavioral personality changes after brain injury are direct consequences of, mainly frontal, neuropathological damage and can be separated from the emotional distress, which is a reaction to the brain injury. Our finding of two distinctive factors is in line with previous studies aimed at differentiating these types of behaviors. Both Warriner and colleagues⁹, using the MMPI, and Hibbard and associates,^{11,12} using the Structured Clinical Interview for DSM IV Diagnosis (SCID), were able to discern Axis I mood and anxiety psychopathology profiles from Axis II personality disorder profiles in TBI patients. Koponen and coworkers¹⁹ found that DSM Axis II type personality disorders were associated with the presence of frontal lesions. It seems likely that these AXIS II personality disorders actually represent neurobehavioral changes in patients with TBI because in particular lesions in the orbitofrontal and ventromedial frontal areas are related to neurobehavioral personality changes after brain injury.^{16,18}

Accordingly, it can be seriously questioned whether a DSM classification of neuropsychiatric disorders is suitable to classify these organic personality changes caused by frontal damage in TBI patients. Yeates and colleagues¹⁴ propose a biopsychosocial approach to describe neurobehavioral personality changes after brain injury and argue that these result from deficits in social cognitive abilities, for instance emotion perception, mentalizing, and emotion regulation. Deficits in social cognition have been demonstrated extensively in moderate to severe TBI patients.^{15,32,33} Moreover, deficits in emotion perception were found to be significantly correlated to the presence of frontal lesions on MRI after TBI¹⁵ as well as to the presence of behavioral changes.³³ Consequently, we expected neurobehavioral changes in the present patient group to be related to frontal damage on CT, which we indeed found.

The presence of frontal damage on CT was not related to affective changes. In a previous study³⁴ no differences were found between patients with minor, mild, moderate, or severe TBI regarding the presence of affective problems (anxiety and depression). If affective problems were related to frontal damage, which is in turn related to injury severity, higher levels should be expected in the moderate and severe groups.¹⁵ However, Fedoroff and associates³⁵ actually found the opposite; the presence of frontal lesions in TBI patients was associated with a diminished likelihood of depression. Fleminger and coworkers³⁶ conclude that depression after brain injury is positively related to insight. On the other hand, behavioral changes, social cognition deficits, and frontal damage after TBI are all related to impaired self-awareness.^{21,22,33} For that

reason, we used proxy ratings as a more accurate indication of the actual status of the patient. For the Affect scale we found no significant difference between patient and proxy rating as opposed to the Behavior scale and Anger scale where proxies indicated more problems than patients. Moreover, correlations between the Behavior and Affect scales were both low for patients and proxy scores, indicating that presence of neurobehavioral problems was only modestly related to presence of affective problems. We conclude therefore that patients in the present group had diminished self-awareness with regard to neurobehavioral changes but not to affective problems.

With regard to Anger, the factor analysis yielded that this was not exclusively part of the neurobehavioral domain, as we expected beforehand. Anger is considered a major characteristic of the neurobehavioral syndrome, resulting from diminished impulse and aggression control, which is related to the integrity of orbitofrontal circuits.¹⁸ However, Williamson and colleagues³⁷ mention anger also as a prominent symptom of post-traumatic stress disorder, which is primarily an anxiety disorder prevailing also in TBI irrespective of injury severity or presence of frontal lesions. Several studies demonstrated a close relationship between anger and depression, in particular reduced frustration tolerance, in healthy populations.^{38,39} These latter findings suggest that anger might be related to affective changes as well. Indeed, we found that Anger had equally high loadings on the Behavior and the Affect scale indicating a relation to the occurrence of both types of problems. However, also for Anger we found a significant difference between patients with and without frontal lesions on early CT. Moreover, logistic regression analysis showed that the presence of frontal lesions was the only significant predictor of Anger, with an OR of more than 3. Apparently, anger is part of both the neurobehavioral and affective domain, but its expression, as observed by proxies, clearly has a relation to disruption of frontal circuits.

Additional validation that the six scales that we found represented different constructs was accomplished by calculating correlations with outcome determined by an experienced neurologist at one year post-injury. We found that the proxy rating of neurobehavioral problems showed the highest correlations with both GOSE and DOS scores, with marked lower correlations of the Behavior-patient scale, the Anger and Affect patient and proxy scales with these outcome measures. Moreover, the Behavior-proxy rating of long-term neurobehavioral problems was in accordance with the neurologist rating of behavioral problems at one year post-injury, represented by the DOS Behavioral subscale. However, with regard to Return to Work in the long term both neurobehavioral changes as indicated by a relevant other as well as affective changes indicated by patients themselves and their proxies appeared to be related to inability to completely return to work. Surprisingly, the presence of frontal lesions did not show substantial correlations with any of these measures except for the DOS Behavioral subscale. Although there was no direct relation between the presence of frontal lesions and Return to Work, we conclude that an indirect relationship between these variables is likely to be mediated by behavioral changes, as indicated by the Behavioral-proxy scale showing significant and substantial correlations with frontal lesions as well as with Return to Work.

We found presence of frontal lesions on CT to be a strong predictor of neurobehavioral changes. However, CT is considered a less sensitive method with lower spatial resolution than MRI. CT is suitable to identify hemorrhagic contusions. For nonhemorrhagic lesions or those smaller than 5 mm, like the small petechial hemorrhages indicating diffuse axonal injury (DAI), MRI has better

diagnostic sensitivity.^{26,27} By using only CT data, it might be possible that some TBI patients are incorrectly classified as having no frontal damage. Hence, using MRI data might have predicted neurobehavioral problems even better. Van der Naalt and associates²⁵ compared early CT with MRI at 3 months. MRI showed lesions in 25% of the patients with normal CT; these “new” lesions were all located in frontotemporal areas. Nevertheless, both for early CT and MRI the presence of frontal abnormalities was related to poor outcome. Skandsen and coworkers⁴⁰ found that MRI only had a prognostic value in the prediction of outcome in severe but not in moderate TBI patients. Yuh and colleagues⁴¹ found that both early CT and MRI had a significant contribution to a prognostic model of outcome. A large drawback of MRI is that it cannot be done on admission and is much more expensive than CT. Consequently, in clinical practice MRI data are not available in the acute stage and can only be collected for a part of the patients in the chronic stage. Taking availability into account and considering that CT abnormalities also have substantial predictive value for outcome, we deem early CT frontal abnormalities the best available predictor of neurobehavioral problems.

There are some limitations to this study. Because patients were approached in the context of an aftercare survey, they were sent only one single questionnaire with a small set of questions to increase response rates, instead of well-known validated questionnaires for affective or neurobehavioral problems. However, these questions were based on the most often described changes and their construct validity was confirmed by means of the factor analysis.

Even so, based on the present results we conclude that the presence of early CT frontal abnormalities in patients with moderate and severe TBI entails a serious risk for developing neurobehavioral problems. Informing patients and their families timely about this risk will allow them to seek early treatment, which might diminish negative consequences in the long term.

Author Disclosure Statement

No competing financial interests exist.

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