J Head Trauma Rehabil

Neuropsychiatric Disorders in Persons With Severe Traumatic Brain Injury: Prevalence, Phenomenology, and Relationship With Demographic Clinical and Functional Features

Paola Ciurli, PsyD; Rita Formisano, PhD, MD; Umberto Bivona, PhD, PsyD; Anna Cantagallo, MD; Paola Angelelli, PhD

Objective: This study aimed to characterize neuropsychiatric symptoms in a large group of individuals with severe traumatic brain injury (TBI) and to correlate these symptoms with demographic, clinical, and functional features. **Methods:** The Neuropsychiatric Inventory (NPI), a frequently used scale to assess behavioral, emotional, and motivational disorders in persons with neurological diseases, was administered to a sample of 120 persons with severe TBI. Controls were 77 healthy subjects. **Results:** A wide range of neuropsychiatric symptoms was found in the population with severe TBI: apathy (42%), irritability (37%), dysphoria/depressed mood (29%), disinhibition (28%), eating disturbances (27%), and agitation (24%). A clear relationship was also found with other demographic and clinical variables. **Conclusion:** Neuropsychiatric disorders constitute an important part of the comorbidity in populations with severe TBI. Our study emphasizes the importance of integrating an overall assessment of cognitive disturbances with a specific neuropsychiatric evaluation to improve clinical understanding and treatment of persons with TBI. **Key words:** *neuropsychiatric disorders*, *Neuropsychiatric Inventory*, *severe traumatic brain injury*

NEUROPSYCHIATRIC SEQUELAE are widely reported in persons with traumatic brain injury (TBI) and their presence and persistence often have deleterious effects on recovery and rehabilitation outcomes. Furthermore, neuropsychiatric symptoms, including disorders of cognition, mood, motivation, and behavior,[1] appear to have an important role in shaping long-term outcomes, particularly those related to family and social reintegration and return to work.[2,3]

The literature on TBI contains a wealth of case reports and retrospective studies. However, there are very few prospective studies, most of which were carried out without using clearly defined criteria or structured instruments.[4] In this area, there are 2 kinds of studies: one tries to assess and find a full spectrum of psychiatric syndromes by using scales that provide a psychiatric diagnosis according to *International Classification of Diseases, Tenth Revision*, or *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) criteria[5–7]; the other uses a dimensional approach to characterize single disturbances such as agitation, disinhibition, apathy, and depression.[8–10] With regard to mood disorders, depressive symptoms,[9,11,12] apathy,[13–15] and anxiety[1] are prevalent; mania[4] and obsessive-compulsive disorder[6] are reported less frequently. Moreover, in the acute recovery period, agitated behavior (ranging from restlessness to aggressiveness) is frequently reported.[16] Although this behavior tends to disappear prior to the resolution of posttraumatic amnesia,[17] it may also continue into the chronic phase.[18,19] Psychosis, which is relatively rare, can also be a serious complication in individuals with TBI.[20] In this population of patients, neurobehavioral disturbances are not only reported in the first phase of the recovery period but may also persist as long-term psychiatric sequelae.[20–22] Furthermore, mood and behavioral disorders interfere with rehabilitation efforts and can result in unemployment, repeated hospitalization, legal problems, and alienation from family and friends.[10] Therefore, these disorders must be identified

Author Affiliations: *IRCCS Santa Lucia Foundation, Rome (Drs Ciurli, Formisano, and Bivona); Department of Neuroscience/Rehabilitation, Hospital and University of Ferrara, Ferrara (Dr Cantagallo); and Department of Psychology, University of Bari, Bari (Dr Angelelli), Italy.*

Corresponding Author: *Paola Ciurli, PsyD, IRCCS Santa Lucia Hospital, via. Ardeatina 306, Rome, Italy (p.ciurli@hsantalucia.it).*

by means of specific assessments.[6] In this way, effective treatments can be undertaken, leading to improved outcomes for individuals with TBI.

Assessing the neuropsychiatric disturbances of persons with brain injuries presents unique challenges.[1,4] Essentially, 4 factors have to be considered.[23] The first is that cognitive deficits (such as memory or language disturbances) and difficulty with self-monitoring and self-awareness, which are frequently associated with TBI, may alter neuropsychiatric assessments and force clinicians to look for other more reliable sources of information.[24] The second factor concerns diagnostic classification, which is usually based on the *DSM-IV*[25] criteria and generically separates psychiatric disorders into "primary" syndromes and "secondary" disorders (ie, associated with general medical conditions); moreover, it does not include phenomenology and specific neuropsychiatric disorders that are very common in populations with TBI such as apathy, irritability or agitation, and disinhibition. The third factor concerns the limited applicability of traditional diagnostic tools in a neurological population. These tools often consist of self-reports, which are inappropriate for persons with TBI, and standardized psychiatric interviews, which are often inadequate for persons with brain injuries because they were developed for psychiatric syndromes not for specific neuropsychiatric symptoms.[26] Finally, the fourth factor is that neurological and cognitive symptoms (such as hypoarousal, loss of energy, and neurovegetative disorders) often mimic or alter the clinical presentation of some psychiatric disturbances,[4,23] which are generally interpreted as somatizations of depression and anxiety.

In recent years, the importance of using specific neuropsychiatric tools that can measure the emotional and behavioral disturbances commonly observed after TBI has been underscored. New clinical tools have been developed[23] that permit detection and quantification of a wider range of neuropsychiatric changes. They are generally based on information gathered from caregivers because of the unreliability caused by deficits in cognition and insight, as well as unawareness. Cummings et al[27] developed the Neuropsychiatric Inventory (NPI), which provides a comprehensive assessment of psychopathology. It consists of an informant-based interview that evaluates behavioral changes secondary to a neurological illness. It covers a wider range of neuropsychiatric symptoms than other tools and minimizes administration time. The authors validated its use in persons with dementia with different etiologies. More recently, the NPI was used successfully to describe the neuropsychiatric symptoms poststroke[23] and of a small cohort of persons with TBI.[28] The use of specific scales, such as the NPI, should increase the sensitivity of clinical observations and facilitate the assessment of neuropsychiatric symptoms.

In this study, we aimed to quantify and characterize neuropsychiatric disorders following severe TBI by using the NPI: (*a*) to obtain a comprehensive description of psychiatric disorders and (*b*) to study the clinical variables that predict the development of emotional and behavioral disorders after severe TBI.

MATERIALS AND METHODS

Participants

This multicenter study included a population of 120 subjects with severe TBI, admitted as in- or outpatients to the rehabilitation programs of the Santa Lucia Foundation (Rome, Italy) and the Department of Neuroscience, Rehabilitation Hospital (Ferrara, Italy), from February 2007 to January 2008. The study was approved by the local ethical committee.

The study sample was from an overall group of 136 persons with TBI admitted to these 2 rehabilitation hospitals. After enrollment, 9 persons with TBI were excluded because they, or their caregivers (7 cases), refused to provide informed consent; 6 persons with TBI were excluded because their caregivers were unreliable because of psychiatric disorders (2 cases) or to alcohol abuse (2 cases) or because they had a very low socioculture level (2 cases); 2 persons with TBI could not participate in the study because they were unexpectedly discharged; and 1 participant was excluded after providing informed consent because his caregiver did not want to continue the study because of psychological distress experienced during the interview. Finally, a total of 96 inpatients (80%) and 24 outpatients (20%) (specifically, 89 males [74.2%] and 31 females [25.8%]) met the inclusion criteria and were enrolled consecutively.

Inclusion criteria required a diagnosis of severe TBI (Glasgow Coma Scale score $\leq$8)[29] medically documented by computerized tomography (CT) or magnetic resonance imaging (MRI) data; Levels of Cognitive Functioning Scale (LCF-S)[30] score of 4 or more; age of at least 15 years at the time of injury; time interval from head trauma longer than 30 days; and provision of informed consent by both the person with severe TBI (or a legal representative) and by his or her caregiver. Subjects were excluded if they had a history of alcohol or drug abuse or if they already had psychiatric or neurological diseases prior to the severe TBI. Subjects who were already on antipsychotic, antidepressant, or anxiolytic drugs were also excluded.

Procedures

Demographic information (age, gender, and years of education) and injury severity data were collected by investigating medical records and by interviewing subjects and family members. All cases were submitted to careful

TABLE 1 *Demographic, clinical, and functional features of the persons with traumatic brain injury (TBI) and healthy controls*

	TBI group ($N = 120$)		Healthy controls ($N = 77$)	
Demographic features	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**
Age, y	31.3 ± 12.7	15–64	36.1 ± 12.9	15–65
Education, y	11 ± 3.5	3–18	12.6 ± 3.9	3–18
Gender distribution, *n*				
Male	89		42	
Female	31		35	
Neurological features				
Chronicity, mo	10.6 ± 15.1	1–73		
TFC, d	22.4 ± 17.0	0–80		
	TBI group, *n*			
Neuroimaging features				
Pure DAI	46			
Focal unilateral or bilateral lesions	38			
DAI with unilateral or bilateral focal lesions	36			
Functional features				
Glasgow Outcome Scale score				
3	69			
4	32			
5	19			
Levels of Cognitive Functioning Scale score				
4–5–6	52			
7–8	68			

Abbreviations: DAI, diffuse axonal injury; TFC, time from injury to when a person is able to consistently follow simple commands.

neuropsychiatric evaluation by a neuropsychologist. A neurologist administered the following scales to assess disabilities and functional recovery status: the Glasgow Outcome Scale (GOS),[31] divided into 3 levels: severe disability (a score of 3), moderate disability (a score of 4), or good recovery (a score of 5) and the LCF-S,[30] with scores ranging from 4 (confused/agitated) to 8 (purposeful/appropriate).

Clinical variables included the interval (in days) from coma onset until the person was able to follow simple commands[32] (TFC) and the interval from the TBI to the NPI evaluation (chronicity, coded as $0 \leq 12$ months and $1 > 12$ months) (Table 1). TFC was established both from clinical reports of the acute and postacute phases and from caregivers' interviews. Subjects were identified as having severe TBI if their TFC was more than 6 hours,[29,33] their GCS score was 8 or less,[29] and whether they presented objective neurological findings (such as altered mental status, cranial nerve deficits, or limb paresis) and/or neuroimaging lesions (focal or diffuse). Although it has been demonstrated that the duration of posttraumatic amnesia is a significant clinical predictor of global and neuropsychological outcomes even when measured retrospectively,[34,35] this marker was not included because it was unavailable for some persons, unreliable in those with persistent memory problems, and still present in others. Two blinded neurologists diagnosed the available cerebral CT scan or MRI as (*a*) diffuse axonal injury (DAI), (*b*) unilateral/bilateral focal lesions, or (*c*) mixed features of unilateral/bilateral focal lesions and DAI. Cerebral lesions were diagnosed as focal when they were larger than 1 cm. Diffuse axonal injury was diagnosed when microscopic (<1 cm) and multiple lesions were present, based on the international literature on DAI.[36–40]

Seventy-seven age-matched, healthy volunteers served as control subjects. They were recruited outside the hospital and were included only if they presented no prior neurological or psychiatric disorders or reduced cognitive efficiency. We included healthy control participants to avoid overestimating neuropsychiatric symptoms in the population with TBI since at least some of the disturbances assessed by the NPI (such as dysphoria/depressed mood, anxiety, irritability, and nighttime/eating disturbances) can also be present in neurologically undamaged people. Table 1 shows the demographic, clinical, and functional features of the population with severe TBI and the demographic data of the healthy controls.

Psychiatric assessment

A close relative of each enrolled person with a brain injury and of each healthy control subject was interviewed using the 12-subscale version of the NPI. This

tool has been validated in an Italian Alzheimer disease population[41] and demonstrated applicability to different populations of persons with brain injury.[23,28] Finally, the NPI has been shown to have good content and concurrent validity as well as adequate test-retest, between-rater reliability, and internal consistency.[27] The Italian version of the NPI has demonstrated comparable psychometric properties.[41] A neuropsychologist in each center administered the NPI to all TBI subjects' caregivers (when the former were admitted to our neuropsychological department) and to each control subject's relative. All subjects with TBI were interviewed before they started taking medications that act on the central nervous system, except for antiepileptic drugs if needed or if already prescribed in the intensive care unit or the neurosurgery unit.

The NPI[27] can investigate the behavioral and mood changes of persons with Alzheimer disease[42] and persons having a stroke[23] in different phases of their diseases. Each subscale assesses a different area: delusions, hallucinations, agitation/aggression, dysphoria/depressed mood, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor behavior, nighttime disturbances, and appetite/eating disturbances. The NPI consists of screening questions to help the relative determine whether behavior changed after the TBI and whether the altered behavior were present at the time of the interview ("in the current week"). If they respond positively, the symptom is explored by means of several subquestions focused on specific features of each disturbance. Symptom *severity* ranges from 1 (mild) to 3 (severe) and *frequency* from 1 (rarely) to 4 (very frequently) on the basis of the relative's estimation. Severity is mainly rated according to pervasiveness of the disturbance. Frequency is rated according to daily, weekly, or monthly recurrence. Typical screening questions are as follows: "Does your husband/wife seem more irritable to you now than before the head trauma? Has he/she ever shouted or cursed in anger?"[27] If the relative responds positively, the original protocol procedure is followed to rate severity and frequency of the disorder. The score for each behavioral domain is the product of the frequency and severity subscore for that particular behavior (maximum 12). Adaptation for normal controls required substitution of the term *brain-injured person* with *your relative* and *after the head trauma* with *this week*.

Data analysis

Because of the ordinal nature of the scale, the neuropsychiatric data were analyzed using several nonparametric tests. The analysis consisted of a preliminary description of NPI score distribution in the sample of participants with severe TBI. To obtain an estimation of symptom incidence in the population with TBI, for each NPI subscale, we computed the percentage of subjects with scores above the 95th percentile of the controls' distribution scores. In this way, we considered as clinically relevant only those scores that were above the control subjects' cutoffs. Then, to understand the phenomenology of the disturbances for each symptom, we computed the percentage of the various specific features that characterized it (ie, for apathy: decrease in activities, loss of interest in plans of family members, or other relevant people, etc). Bootstrap analysis was performed to compare between-group means. In fact, because of the nonnormal distribution of the composite NPI scores (multiplying frequency [1–4] by severity [1–3], subscores would not produce a 5, 7, or 11 composite score) and the nonnormal distribution obtained in our samples (distribution of the controls' scores was very skewed considering that 95% of them scored below 1), traditional parametric analyses were precluded and the nonparametric Kruskal-Wallis or Mann-Whitney *U* tests resulted in a loss of power.

Bootstrap analysis is a nonparametric resampling technique that allows a probability function based on the data set actually obtained in the population. It combines the scores of the samples studied into a unique pool of data from which it extracts a number of groups equal to the original number (in the present case, 4). Mean differences are then calculated from the randomly constituted groups. These operations (resampling and mean difference computation) are repeated on the data set 3000 times to produce a distribution of the possible mean difference for each NPI subscale. For each possible value obtained, the probability is then computed by the frequency distribution. If the observed difference is more than 95% of the expected difference from random resampling, it is judged to be significant at the .05 level.

To evaluate the role of other demographic, clinical, and functional variables in predicting the occurrence of various neuropsychiatric symptoms, a logistic regression analysis (forward stepwise) was performed using the various NPI symptoms (coded as 1 = present and as 0 = absent) as dependent variables and 7 different independent variables (age, education, gender, chronicity, TFC, GOS scores, and neuroimaging data) coded as described previously.

RESULTS

NPI: Incidence and phenomenology of symptoms

For each NPI subscale, Table 2 reports the scores corresponding to the 95th percentile of the control population, the number (and corresponding proportion) of subjects with brain injuries who obtained scores above the controls' cutoffs (ie, the proportion of patients showing clinically relevant disturbances). A preliminary

TABLE 2 *Prevalence of neuropsychiatric symptoms in the population with traumatic brain injury*

Symptom	Healthy controls >95th percentile	No. patients >95th percentile	% Patients >95th percentile
Delusions	0	17	14
Hallucinations	0	9	8
Agitation/aggression	2	29	24
Dysphoria/depressed mood	2	35	29
Anxiety	6	9	8
Euphoria	0	16	13
Apathy	1	50	42
Disinhibition	0	33	28
Irritability/lability	1	44	37
Aberrant motor behavior	0	11	9
Nighttime disturbances	1	18	15
Appetite/eating disturbances	2	32	27

exploration of the table shows important qualitative differences between participants with TBI and healthy controls. In the TBI population, positive cases were recorded for delusions, hallucinations, euphoria, disinhibition, and aberrant motor behavior; in contrast, not one of these disturbances was recorded in controls. Moreover, several subjects with TBI presented scores exceeding controls' cutoffs for anxiety, dysphoria/depressed mood, agitation, irritability, apathy, and appetite/nighttime disturbances. In terms of prevalence, the most common neuropsychiatric symptom in subjects with TBI was apathy, exhibited in 42% of the cases, followed by irritability (37%), dysphoria/depressed mood (29%), disinhibition (28%), appetite/eating disturbances (27%), agitation/aggression (24%), nighttime disturbances (15%), and delusions and euphoria (14% and 13% respectively) and more rarely (10%) by aberrant motor behavior (9%), hallucinations (8%), and anxiety (8%). Table 3 shows the phenomenology characterizing the most frequent symptoms of each disturbance.

Comparison between persons with severe TBI and healthy controls

Table 4 shows the mean composite neuropsychiatric score for each symptom in persons with severe TBI and healthy controls. In the TBI group several neuropsychiatric symptoms resulted significantly present: delusions, agitation, dysphoria/depressed mood, apathy, disinhibition, irritability and appetite/eating disturbances (all $P <$ .001), euphoria, aberrant motor behavior and nighttime disturbances (all $P < .01$). For hallucinations and anxiety the analysis of mean failed to highlight higher scores in TBI population with respect to controls. Results of these analysis suggested that the group with severe TBI was significantly disturbed by several neuropsychiatric symptoms.

Relationship with other demographic or clinical features

Table 5 shows significant results of the multiple logistic regression analysis. Dysphoria/depressed mood and nighttime disturbances were significantly associated with age. Older persons with TBI had a higher risk of developing depressive symptoms and nighttime disturbances than younger persons with these injuries. Irritability was linked with chronicity. Persons with TBI at 1 year from the onset of severe TBI had a greater risk of becoming irritable. Aberrant motor behaviors and anxiety were significantly associated with focal lesions. In particular, persons with TBI and focal unilateral or bilateral lesions had a 9 times greater risk of developing aberrant motor behaviors and a 4 times greater risk of developing anxious behaviors than the other persons with TBI. None of the other more frequent disorders were associated with any other lesion site or injury features. Finally, apathy and disinhibition were associated with GOS score severity. Persons with TBI and a GOS score of 3 had a 4 times greater risk of developing apathetic behaviors and a 3 times greater risk of developing disinhibition than the other injured persons.

DISCUSSION

The aims of the present study were to obtain a comprehensive description of psychiatric disorders in a population with severe TBI by using the NPI and to identify the demographic, clinical, and functional variables that can predict the development of emotional and behavioral disorders in this population. After severe TBI, at least 1 of the 12 investigated neuropsychiatric symptoms was found to be clinically relevant in 78% of persons with TBI. The most frequent neuropsychiatric disorders in our sample of participants with severe TBI were apathy,

TABLE 3 *Phenomenology of most frequent symptoms*

Neuropsychiatric Inventory domains	Symptoms	%
Apathy	Decrease in activities	76
	Loss of interest in family members' or other relevant people's plans	76
	Inattention to usual interests	70
	Reluctance to start a conversation	67
Irritability/lability	Enhanced impatience and nervousness	75
	Outbursts of anger	63
	Impatience for delays or planned activities	50
Dysphoria/depressed mood	Crying episodes and sadness	77
	Pessimism	69
	Feeling of uselessness and being a burden on family members	54
	Suicidal ideas	54
Disinhibition	Acting impulsively	58
	Speaking confidentially with unfamiliar people	53
	Being tactless and offensive	34
Appetite/eating disturbances	Alterations of eating habits (eg, preferred food or putting too much food in the mouth)	47
	Enhanced appetite	42
Agitation/aggression	Obstinacy	77
	Noncompliance, refusal to cooperate with the caregiver	77
	Screams and imprecations	70
	Violence toward objects and even people	54
Nighttime disturbances	Awaking during the night	50
	Difficulties in falling asleep	33
	Inadequate behaviors such as getting up and wandering around the house	33
	Sleeping during the day	33
Delusions	Illogical belief that relatives or other people lie on their true identity	50
	Persuasion that someone was conspiring against them and felt in anger that family members would leave them	30
Euphoria	Childish humor	63
	Tendency to find things ridiculous that were not	50
	Sense of unmotivated well-being or happiness	38
Aberrant motor behavior	Walking without a goal	50
	Repeating movements such as going back and forth on the wheelchair	50
Hallucinations	Referring things not present	60
	Speaking with imaginary people	40
Anxiety	Excessive preoccupation about programmed events	40
	Separation anxiety	40
	Subjective tension and inability to relax	30
	Anxiety related to specific places (socially frequented) or situations (eg, cars)	30

followed by irritability, dysphoria/depressed mood, disinhibition, appetite/eating disturbances, and agitation/aggression. Although it is not easy to compare our results with those of previous studies on populations with TBI because of the different approaches used (*DSM-IV* classification or rating scales evaluating single symptoms), they confirm the high frequency and wide range of neuropsychiatric disturbances in populations with severe TBI.

The high frequency of apathy in our sample of participants with TBI is in line with the findings of other studies that assessed adults with TBI using the Apathy Evaluation Scale,[13] in which the average rate of apathy was 61.4%, with the lowest prevalence of 46.4%[43] and the highest of 71.1%.[15] It is well known that loss of motivation impairs rehabilitation outcomes and coping skills[44] and that it is one of the most common problems for persons with TBI and their families.[45] Nevertheless, unlike reports in previous studies, here apathy was not correlated with gender,[46] chronicity,[47] or injury severity.[15,46]

Regarding symptoms of depression and anxiety, the frequency of occurrence of both symptoms in the present and previous research deserves some comments. Dysphoria/depressed mood was found in 29% of persons with TBI in our sample, whereas in previous studies,[1,48] the incidence of depression ranged from 6% to 77%. Similarly, positive scores on the anxiety subscale were found in 8% of participants in our sample, whereas anxiety was reported to range from 11% to

TABLE 4 *Mean Neuropsychiatric Inventory composite scores of healthy controls and persons with traumatic brain injury (TBI)*[a]

Symptoms	Healthy controls ($n = 77$)	Persons with TBI ($n = 120$)
Delusions	0.000	0.692*
Hallucinations	0.000	0.250
Agitation/aggression	0.260	1.942*
Dysphoria/depressed mood	0.273	2.067*
Anxiety	1.156	1.108
Euphoria	0.000	0.550**
Apathy	0.208	3.458*
Disinhibition	0.000	1.042*
Irritability/lability	0.117	2.342*
Aberrant motor behavior	0.000	0.567**
Nighttime disturbances	0.299	1.075**
Appetite/eating disturbances	0.403	1.692*
Total score	2.714	16.783*

[a]Comparison with healthy controls: *$P < .001$; **$P < .01$.

70% in other investigations of TBI.[1,48] These variations can be explained by methodological differences. Most studies used the *DSM-IV* or research diagnostic criteria. The diagnosis of depression according to *DSM-IV* is based on clusters of symptoms that vary in number according to the different subtypes of depression; moreover, many of these symptoms are somatic or motivational and in TBI may occur independently of their effects on mood disorders. For example, fatigue, sleep disturbances, and concentration difficulties are common signs and symptoms in TBI with and without mood disorders.[4,49]

In contrast, the dysphoria/depressed mood domain of the NPI excludes features common to both TBI and depression (ie, vegetative symptoms) and includes more specific mood changes than other tools based on the *DSM-IV* diagnostic criteria.[50] Indeed, we found a higher frequency of apathy than dysphoria/depressed mood in our sample of participants with severe TBI. Moreover, even if the different apathy and depression evaluation scales are often correlated,[51] these 2 symptoms have to be clinically differentiated. In fact, Andersson et al[52] found that although apathy and depression share common clinical features (reduced initiative, lack of emotional responsiveness, and inattention), they can occur independently. In fact, apathy was not correlated with depressed mood, which is one of the main symptoms of depression. The NPI subscores for apathy and dysphoria/depressed mood confirm what we commonly observe with severe TBI in our practice.

As for phenomenology, in our study, dysphoria/depressed mood was manifested mostly by crying episodes and sadness, pessimism and feelings of uselessness, being a burden on family members, and, finally, suicidal ideas. These data are in line with the interesting results of Jorge and colleagues.[11] These authors examined the evolution of psychological and somatic symptoms over the course of 1 year in 66 subjects with TBI and found that 4 symptoms consistently differentiated depressed from nondepressed persons: depressed mood, reduced energy, feelings of worthlessness, and suicidal ideation.

It stands to reason that a person who is experiencing apathy or dysphoria will manifest lower functioning with regard to collaboration in rehabilitation or in the activities of daily living because of pessimism or a loss of motivation. Both the high frequency of these passive behavioral features (apathy and depressed mood) and the kind of phenomenology associated with these disturbances, such as decreased activities, loss of interest in others, neglecting usual interests, sadness, and pessimism, may explain the high level of family distress and the poor functional outcome in terms of social reintegration and school/work reentry. All these symptoms affect participation in daily living activities, which is the strongest predictor of life satisfaction,[53] and the ability to get along with people, to afford things, and to engage in work and leisure.[54] We also detected the typical positive symptoms of severe TBI such as irritability, disinhibition, agitation/aggression, and, less frequently, euphoria, aberrant motor behavior, delusions, and hallucinations. Although other studies have reported similar disturbances, comparisons are often impossible because some authors diagnosed these symptoms as psychotic[48,55] or manic[6,56,57] whereas others focused only on single disturbances such as agitation[19,58] or aggression.[4,59,60] For example, irritability is often considered a single symptom of broader syndromes such as mania,[56] bipolar disorders,[61] or postconcussive syndromes.[62] Moreover, most studies do not report base rates of psychiatric symptoms in healthy controls, although symptoms such as irritability, anxiety, and depressed mood may also be present as situational or reactive conditions in these subjects. For this reason, we decided to enroll a control group of normal subjects.

With regard to the influence of age, we found that older persons with TBI were at higher risk of developing depressed mood and nighttime disturbances. Consistently with these findings, previous studies[63,64] reported statistically significant correlations between age and likelihood of depression (ie, depression has been found to be more frequent with increasing age). Conversely, Deb and Burns[65] found that depressive disorders were more common in younger persons with TBI than in older ones, but the age difference was not statistically significant.

TABLE 5 *Multiple logistic regression results*[a]

Variables	NPI symptoms	
Age	Dysphoria/depressed	OR = 1.04, 95% CI = 1.00–1.07, accuracy in prediction 63%, significance of model $\chi^2 = 8.18$, $P = .01$
	Nighttime disturbances	OR = 1.04, 95% CI = 1.00–1.08, accuracy in prediction 84,8%, significance of model $\chi^2 = 4.26$, $P < .05$
Chronicity	Irritability/lability	OR = 1.11, 95% CI = 1.33–6.36, accuracy in prediction 71.4%, significance of model $\chi^2 = 16.64$, $P = .001$
Focal lesion	Aberrant motor behavior	OR = 9.42, 95% CI = 1.83–48.32, accuracy in prediction 91.4%, significance of model $\chi^2 = 9.04$, $P = .001$
	Anxiety	OR = 4.09, 95% CI = 1.59–10.48, accuracy in prediction 76.2%, significance of model $\chi^2 = 8.71$, $P = .001$
Glasgow Outcome Scale severity	Apathy	OR = 3.77, 95% CI = 1.62–8.73, accuracy in prediction 64.8%, significance of model $\chi^2 = 10.27$, $P = .001$
	Disinhibition	OR = 2.84, 95% CI = 1.04–7.83, accuracy in prediction 74,3%, significance of model $\chi^2 = 4.57$, $P = .05$

Abbreviations: CI, confidence interval; NPI, Neuropsychiatric Inventory; OR, odds ratio.
[a]Significant relations between NPI symptoms and other demographic, clinical, and functional variables.

Moreover, unlike our study, which evaluated a sample of participants with severe TBI ranging in age from 15 to 65 years, these authors split their participants into 2 age groups, that is, 18 to 65 years and older than 65 years. Because of these methodological differences, our results cannot be compared with those of Deb and Burns.[65]

Older age was also found to correlate with nighttime disturbances, which are generally taken into account by different evaluation scales to diagnose depression. Since increased levels of anxiety and depression are commonly associated with sleep disturbances,[66] the similar correlation found between nighttime disturbances and older age should be considered an expected result, as secondary correlation with depressed mood. However, a recent study[67] did not find any statistically significant correlation between age and sleep disturbance; however, it showed that this symptom is a very common problem (70%) in all persons with closed-head injury.

As far as clinical variables are concerned, chronicity has been found to significantly correlate with irritability. In fact, persons at 1 year from the onset of severe TBI had a higher risk of becoming irritable. These data likely have 2 explanations: (*a*) the association of greater time postinjury with greater reporting of irritability suggests that caregivers' awareness of such problems increased with increasing exposure, and (*b*) that the difficulties experienced by persons with TBI in their family and social reintegration or in school or work reentry may have increased irritability. Also, other authors[1] found that behavioral deficits not only persisted in the population with TBI but also became even more severe with passing time, probably because of exposure to stressful factors associated with daily life changes and the coping process.

Our finding of a significant correlation between the presence of focal lesions and the risk of developing aberrant motor behavior is consistent with the data reported by Van Der Naalt et al.[68] These authors used CT and MRI along with a prospective investigation of the relationship between early behavioral disturbances and cerebral abnormalities on imaging studies in 67 subjects with mild to moderate TBI. In this latter study,[68] CT focal lesions were diagnosed in 81% of the persons with mild TBI and in 100% of the persons with moderate TBI who were restless or agitated. Similarly, late MRI imaging revealed focal lesions in most of the participants in our sample. Most frequently, individuals with TBI and early behavioral disturbances present lesions of the frontotemporal lobes. Thus, subjects with restlessness and agitation have likely suffered focal brain damage.[68] Moreover, in agreement with previous imaging studies,[69,70] residual emotional disturbances reported 1 year after injury were associated with focal cerebral lesions. In our study, DAI was present in most persons with TBI, although cerebral MRI was not available for all enrolled subjects. As it is well known that CT scans can detect DAI in only about 50% of persons with TBI[71] and that these scans are not sensitive to injury-related changes, the lack of any statistically significant correlation between DAI and any clinical or neuropsychiatric features cannot be considered as a conclusive result.

In our study, apathy and disinhibition were significantly correlated with severity of disability (GOS score), which, therefore, may have had a greater impact on final outcomes, social functioning, and reintegration. In fact, the presence of such symptoms in the population with TBI may have considerably affected the possibility of successful family and social reintegration and of

work/study reentry. It is a common issue for the caregiver of persons with TBI to have to deal with behavioral and/or emotional disturbances, which usually cause social isolation.

Regarding disinhibition, a few studies in the literature focused on this symptom, probably because it is included in the psychiatric syndrome of psychosis. Starkstein and Robinson[72] found a statistically significant correlation between the disinhibition syndrome and orbitofrontal and basotemporal lesions after acquired brain injury. The association between disinhibition and worse GOS score confirmed our clinical experience and previous data[73] on poor social outcome; indeed, this kind of "active" disorder may cause social isolation, a loss of friends, and a decrease in intimate and sexual relationships, with consequent worsening in the quality of life of both persons with TBI and caregivers.[73]

Finally, the present study shows that the use of an informant-based interview, such as the NPI, which is based on specific neuropsychiatric disturbances commonly found in neurologically damaged persons, may provide a much broader overview of neuropsychiatric sequelae in a population with severe neuropsychological deficits due to TBI (LCF-S score from 4 to 8). Indeed, these disorders are very difficult to detect by using self-reports because of the presence of deficits in awareness and introspection. Moreover, in the present study, we extended the use of this tool beyond the study of dementia and stroke[23,41] and confirmed the suitability of this kind of interview for use with persons with severe TBI.[28] Finally, because the NPI compares the injured person's condition (before vs after TBI), it allows investigating whether the symptoms can be considered a direct consequence of the trauma per se or a worsening of the person's premorbid personality.

The present study underscores the importance of monitoring severe emotional and behavioral disturbances, which are very frequent, often long-lasting, and a relevant part of the comorbidity of this neurological population. In our sample of participants with TBI, we found a high prevalence of clinically relevant neuropsychiatric disturbances. Further studies including different cohorts of patients (ie, persons without TBI or neurological illness, such as heart disease or orthopedic injury) are needed to determine whether the neuropsychiatric symptoms found in severe TBI are directly correlated with the TBI, with impaired function, or with the trauma per se. Moreover, the methodology for assessing outcomes of persons with TBI must be improved with regard to family, social, and occupational reintegration and perception of the quality of life.

In conclusion, our study emphasizes the importance of integrating an overall assessment of cognitive disturbances with a specific neuropsychiatric evaluation so that all possible comorbidities are considered in the rehabilitation of persons with severe TBI. In this way, disturbances could be treated early and specifically, thus improving collaboration in rehabilitation programs and leading to better long-term psychosocial outcomes, social reintegration, and a higher quality of life for persons with TBI and their families.

REFERENCES

1. Rao V, Lyketsos C. Neuropsychiatric sequelae of traumatic brain injury. *Psychosomatics*. 2000;41(2):95–103.
2. Lippert-Gruener M, Wedekind Ch, Klug N. Functional and psychosocial outcome one year after brain injury and early onset rehabilitation therapy. *J Rehabil Med*. 2002;34:211–214.
3. Warriner EM, Velikonja D. Psychiatric disturbances after traumatic brain injury. *Neurobehav Pers Changes Curr Psychiatry Rep*. 2006;8:73–80.
4. Kim E, Lauterbacch EC, Reeve A, et al. Neuropsychiatric complications of traumatic brain injury: a critical review of the literature (A Report by the ANPA Committee on Research). *J Neuropsychiatry Clin Neurosci*. 2007;19(2):106–127.
5. Deb S, Lyons I, Koutzoukis C, Ali I, McCarthy G. Rate of psychiatric illness 1 year after traumatic brain injury. *Am J Psychiatry*. 1999;156:374–378.
6. Van Reekum R, Bolago I, Finlayson MAJ, Garner S, Links PS. Psychiatric disorders after traumatic brain injury. *Brain Inj*. 1996;10(5):319–327.
7. Koponen S, Taiminen T, Portin R, et al. Axis I and II psychiatric disorders after traumatic brain injury: a 30-year follow up study. *Am J Psychiatry*. 2002;159:1315–1321.
8. Hibbard MR, Uysal S, Kepler K, et al. Axis 1 psychopathology in individuals with traumatic brain injury. *J Head Trauma Rehabil*. 1998;13:24–39.
9. Kreutzer JS, Seel RT, Gourley E. The prevalence and symptom rates of depression after traumatic brain injury: a comprehensive examination. *Brain Inj*. 2001;15:563–576.
10. Rao V, Spiro JR, Schretlen DJ, Cascella NG. Apathy syndrome after traumatic brain injury compared with deficits in schizophrenia. *Psychosomatics*. 2007;48:217–222.
11. Jorge RE, Robinson RG, Arndt S. Are there symptoms that are specific for depressed mood in patients with traumatic brain injury? *J Nerv Ment Dis*. 1993;181:91–99.
12. Kennedy RE, Livingston L, Riddick A, Marwitz JH, Kreutzer JS, Zasler ND. Evaluation of the Neurobehavioral Functioning Inventory as a depression screening tool after traumatic brain injury. *J Head Trauma Rehabil*. 2005;20:512–526.
13. Marin RS. Buedrzycki RC, Firnciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res*. 1991;38:143–162.
14. Marin RS, Wilkotsz PA. Disorders of diminished motivation. *J Head Trauma Rehabil*. 2005;20:377–388.
15. Kant R, Duffy JD, Pivovarnik A. Prevalence of apathy following head injury. *Brain Inj*. 1998;12:87–92.
16. Kim E. Agitation, aggression, and disinhibition syndromes after traumatic brain injury. *Neurorehabilitation*. 2002;17:297–310.
17. Corrigan JD. Development of a scale for assessment of agitation following traumatic brain injury. *J Clin Exp Neuropsychol*. 1988;11:261–277.

18. Silver JM, Hales RE, Yudofsky SC. Neuropsychiatric aspects of traumatic brain injury. In: Yudofsky SC, Hales RE, eds. *The American Psychiatric Press Textbook of Neuropsychiatry*. 2nd ed. Washington, DC: American Psychiatric Association; 1994:313–356.
19. Levy M, Berson A Cook T, et al. Treatment of agitation following traumatic brain injury: a review of literature. *Neurorehabilitation*. 2005;20:279–306.
20. McAllister TW. Evaluation and treatment of neurobehavioral complications of traumatic brain injury–have we made any progress? *Neurorehabilitation.* 2002;17:263–264.
21. Sorenson SB, Kraus JF. Occurrence, severity and outcome of brain injury. *J Head Trauma Rehabil*. 1991;5:1–10.
22. Arciniegas DB, Topkoff J, Silver JM. Neuropsychiatric aspects of traumatic brain injury. *Curr Treat Options Neurol.* 2000;2(2):186–196.
23. Angelelli P, Paolucci S, Bivona U, et al. Development of neuropsychiatric symptoms in post-stroke patients: a cross sectional study. *Acta Psychiatr Scand.* 2004;110:55–63.
24. McAllister TW. Neurobehavioral sequelae of traumatic brain injury: evaluation and management. *World Psychiatry.* 2008;7:3–10.
25. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM).* 4th ed. Washington, DC: American Psychiatric Press; 1995.
26. Brown RG, MacCarthy B. Psychiatric morbidity in patients with Parkinson's disease. *Psychol Med*. 1990;20:77–87.
27. Cummings JL, Mega M, Gray K, Rosemberg-Thompson S, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44:2308–2314.
28. Cantagallo A, Dimarco F. Prevalence of neuropsychiatric disorders in traumatic brain injury patients. *Eur Med Phys*. 2003;38:167–178.
29. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. *Lancet*. 1974;2:81–84.
30. Hagen C, Malkmus D, Durham P. Levels of Cognitive Functioning. In: *Rehabilitation of the Head Injured Adult. Comprehensive Physical Management*. 8th ed. Downey, CA: Professional Staff Association of Rancho Los Amigos Hospital Inc; 1979:87–90.
31. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet*. 1975;1:480–484.
32. Jennett B. Clinical assessment of consciousness [Introduction]. *Acta Neurochir*. 1986;36:90.
33. Kraus MF. Neuropsychiatric sequelae: assessment and pharmacologic intervention. In: Marion DW, ed. *Traumatic Brain Injury*. Vol 14. New York, NY: Thieme Medicine Publishers; 1999:173–178.
34. Wilson BA, Evans JJ, Emslie H, Balleny H, Watson PC, Baddeley A. Measuring recovery from post traumatic amnesia. *Brain Inj.* 1999;13(7):502–520.
35. McMillan TM, Jongen EL, Greenwood RJ. Assessment of post-traumatic amnesia after closed head injury: retrospective or prospective? *J Neurol Neurosurg Psychiatry*. 1996;60(4):422–427.
36. Adams JH, Doyle D, Ford I, Gennarelli TA, Graham DI, McLellan DR. Diffuse axonal injury: definition, diagnosis and grading. *Histopathology*. 1989;15:49–59.
37. Graham DI. Neuropathology of head injury. In: Narayan RK, Wilburger JE, Povlishock JT, eds. *Neurotrauma*. New York, NY: McGraw-Hill; 1996:43–59.
38. Meyhaler JM, Peduzz JD, Eleftheriou E, Novack TA. Current concepts: diffuse axonal injury-associated traumatic brain injury. *Arch Phys Med Rehabil.* 2001;82:1461–1471.
39. Tomaiuolo F, Carlesimo GA, Di Paola M, et al. Gross morphology and morphometric sequelae in the hippocampus, fornix and corpus callosum of patients with severe non missile traumatic brain injury without macroscopic detectable lesions: a T1 weighted MRI study. *J Neurol Neurosurg Neuropsychiatry.* 2004;75(9):1314–1322.
40. Giugni E, Sabatini U, Hagberg GE, Formisano R, Castriota-Scanderbeg A. Fast detection of diffuse axonal damage in severe traumatic brain injury: comparison between gradient-recalled echo (GRE) and turbo (T-Pepsi) MRI sequences. *Am J Neuroradiol.* 2005;26:1140–1148.
41. Binetti G, Mega MS, Magni E, et al. Behavioral disorders in Alzheimer disease: a transcultural perspective. *Arch Neurol.* 1998; 55:539–544.
42. Mega MS, Cummings JL, Fiorello T, Gornbein J. The spectrum of behavioral changes in Alzheimer's disease. *Neurology.* 1996;46:130–135.
43. Craig AH, Cummings JL, Fairbanks L, et al. Cerebral blood flow correlates of apathy in Alzheimer disease. *Arch Neurol*. 1996;53: 1116–1120.
44. Finset A, Andersson S. Coping strategies in patients with acquired brain injury: relationships between coping, apathy, depression and lesion location. *Brain Inj.* 2000;14(10):887–905.
45. Marsh NV, Kersel DA, Havill JH, Sleigh JW. Caregiver burden at 6 months following severe traumatic brain injury. *Brain Inj.* 1998;12:225–238.
46. Glenn MB, Burke DT, O'Neil-Pirozzi T, et al. Cutoff score on the apathy evaluation scale in subjects with traumatic brain injury. *Brain Inj*. 2002;16(6):509–516.
47. Resnick B, Zimmerman SI, Magaziner J, Adelman A. Use of the Apathy Evaluation Scale as measure of motivation in elderly people. *Rehabil Nurs*. 1998;23:141–147.
48. Jorge R, Robinson RG. Mood disorders following traumatic brain injury. *Neurorehabilitation.* 2002;17:311–324.
49. Babin PR. Diagnosing depression in persons with brain injuries: a look at theories, the DSM-IV and depression measures. *Brain Inj.* 2003;17(10):889–900.
50. First MB, Spitzer RL, Gibbon M et al. *Beck Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-1).* New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 1995.
51. Marin RS, Firinciogullari S, Biedrzycki RC. The sources of convergence between measures of apathy and depression. *J Affect Disord*. 1993;28:117–124.
52. Andersson S, Gundersen PM, Finset A. Emotional activation during therapeutic interaction in traumatic brain injury: effect of apathy, self-awareness and implications for rehabilitation. *Brain Inj.* 1999;13:393–404.
53. Pierce CA, Hanks RA. Life satisfaction after traumatic brain injury and the world heath organization model of disability. *Am J Phys Med Rehabil.* 2006;85(11):889–898.
54. Steadman-Pare D, Colantonio A, Ratcliff G, Chase S, Vernich L. Factors associated with perceived quality of life many years after traumatic brain injury. *J Head Trauma Rehabil.* 2001;16(4):330–342.
55. McAllister TW, Ferrell RB. Evaluation and treatment of psychosis after traumatic brain injury. *Neurorehabilitation*. 2002;17:357–368.
56. Shukla S, Cook BL, Mukherjee S, et al. Mania following head trauma. *Am J Psychiatry*. 1987;144:93–96.
57. Starkstein SE, Pearlson GD, Boston J, Robinson RG. Mania after brain injury: a controlled study of causative factors. *Arch Neurol.* 1987;44:1069–1073.
58. Nott MT, Chapparo C, Baguley IJ. Agitation following traumatic brain injury: an Australian sample. *Brain Inj*. 2006;20(11):1175–1182.
59. Greve KW, Sherwin E, Stanford MS, et al. Personality and neurocognitive correlates of impulsive aggression in long-term survivors of severe traumatic brain injury. *Brain Inj*. 2001;15:255–262.
60. Tateno A, Jorge RE, Robinson RG. Clinical correlates of aggressive behaviour after traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. 2003;15:155–160.

61. Zwil AS, McAllister TW, Raimo E. The expression of bipolar affective disorders in brain injured patients. *Int J Psychiatry Med*. 1992;22:377–395.
62. McAllister TW, Arciniegas D. Evaluation and treatment of postconcussive symptoms. *Neurorehabilitation*. 2002;17:265–283.
63. Glenn MB, O'Neil-Pirozzi T, Goldstein R, Burke D, Jacob L. Depression among outpatients with traumatic brain injury. *Brain Inj*. 2001;15:811–818.
64. Levin HS, McCuley SR, Josic CP et al. Predicting depression following mild traumatic brain injury. *Arch Gen Psychiatry*. 2005;62(5):523–528.
65. Deb S, Burns J. Neuropsychiatric consequences of traumatic brain injury: a comparison between two age groups. *Brain Inj*. 2007;21(3):301–307.
66. Parcell DL, Ponsford JL, Rajaratnam SM, Redman JR. Self-reported changes to nighttime sleep after traumatic brain injury. *Arch Phys Med Rehabil*. 2006;87(2):278–285.
67. Makley MJ, English JB, Drubach DA, et al. Prevalence of sleep disturbance in closed head injury patients in a rehabilitation unit. *Neurorehabil Neural Repair*. 2008;22:341–347.
68. Van Der Naalt J, Van Zoomeren AH, Sluiter WJ, Minderhoud JM. Acute behavioural disturbances related to imaging studies and outcome in mild-to-moderate head injury. *Brain Inj*. 2000;14(9):781–788.
69. Oder W, Goldenberg G, Spatt J, Podreka I, Binder H, Deecke L. Behavioural and psychosocial sequelae of severe closed head injury and regional cerebral blood flow: a SPECT study. *J Neurol Neurosurg Psychiatry*. 1992;55:475–480.
70. Ruff RM, Crouch JA, Troster AI, et al. Selected cases of poor outcome following a minor brain trauma: comparing neuropsychological and positron emission tomography assessment. *Brain Inj*. 1994;8:297–308.
71. Mittl RL, Grossman RI, Hiehle JF, et al. Prevalence of MR evidence of diffuse axonal injury in patients with mild head injury and normal head CT findings. *AJNR Am J Neuroradiol*. 1994;15(8):1583–1589.
72. Starkstein SE, Robinson RG. Mechanism of disinhibition after brain lesions. *J Nerv Ment Dis*. 1997;185(2):108–114.
73. Koskinen S. Quality of life 10 years after a very severe traumatic brain injury (TBI): the perspective of the injured and closest relative. *Brain Inj*. 1998;12(8):631–648.