

# Behavioral Changes and Associated Factors After Diffuse Axonal Injury

Debora Souza Sardinha, MSc, RN ■ Rita de Cássia Almeida Vieira, PhD, RN ■

Wellingson Silva Paiva, PhD, MD ■ Daniel Vieira de Oliveira, MD ■ Regina Márcia Cardoso de Sousa, PhD, RN

## ABSTRACT

Diffuse axonal injury (DAI) is a frequent injury after traumatic brain injury (TBI), which causes cognitive and behavioral symptoms. Behavioral changes after DAI affect the patients' quality of life, in addition to causing great damage to their family and society. This study aimed to analyze the behavioral changes of patients with DAI according to family members and to identify the associated factors. This study included patients with DAI, aged between 18 and 60 years, who presented to a referral hospital for traumatic injuries. A prospective cohort study was conducted with 2 evaluations of family members at 3, 6, and 12 months posttrauma. Behavioral changes were evaluated using a questionnaire designed to identify changes according to the perception of family members. The mixed-effects model was applied to identify significant behavioral changes, the effect of time on these changes, and the association between sociodemographic variables, DAI severity, and behavioral changes. Anxiety, dependency, depression, irritability, memory, and mood swings were significantly different ( $p \leq .05$ ) before and after trauma. An analysis of the evolution of these behaviors showed that the changes persisted with the same intensity up to 12 months posttrauma. There was an association between depression and income, age and irritability, and DAI severity and dependency. Unfavorable behavioral changes were frequent consequences of DAI, and no improvement in these changes was noted up to 12 months after the injury. Income, age, and DAI severity were related to behavioral changes.

## Key Words

Behavior, Brain injuries, Diffuse axonal injury, Outcome and process assessment, Social behavioral disorders

Follow-up of patients with traumatic brain injury (TBI) has revealed the presence of physical, cognitive, and behavioral consequences, which, in addition to changing the patients' quality of life, have a great impact on their family and the society (Hora & Sousa, 2005, 2009). Patient outcomes after TBI are primarily described in functional terms with instruments that classify recovery using criteria related to dependency. However, behavioral changes often remain imperceptible to health professionals using these instruments, except in cases of severe changes. In this context, the family is an important informant of these changes because family members have a more appropriate perception of how patients are affected by the trauma by living with them daily before and after the injury. Therefore, the family has the benefit of having known the person before the trauma and after it, interacting in unstructured environments and with high social demand (Hora & Sousa, 2005; Kolitz, Vanderploeg, & Curtiss, 2003; Lippert-Gruner, Kuchta, Hellmich, & Klug, 2006). Faced with this fact, researchers have recognized that family members are generally exceptionally qualified informants to assess behavioral changes after TBI. Patients with TBI underestimate the cognitive and behavioral difficulties, and orientation and concentration disorders may render them unable to complete neurobehavioral tests (Esbjörnsson, Skoglund, & Sunnerhagen, 2013; Kolitz et al., 2003; Lippert-Gruner et al., 2006).

Studies of family members that analyze the behavioral changes of TBI patients have shown that they adopt a broader definition of behavioral changes than those used by most clinical researchers; for example, they consider memory impairment and information processing speed as behavioral changes. For family members, these cognitive alterations directly affect the behavior of patients, indicating that the inclusion of these cognitive disabilities in the conceptualization of behavioral changes is appropriate (Braine, 2011; Tam, McKay, Sloan, & Ponsford, 2015). Frosch et al. (1997), considering the more comprehensive definition adopted by family members, developed a questionnaire that studies the behavioral changes of the patients after the trauma from the family's point of view, implementing a quantitative comparison of aspects such as aggression, anxiety, impulsivity, and memory (among

**Author Affiliations:** Nursing School (Ms Sardinha and Drs Vieira and Sousa); and Division of Neurosurgery (Drs Paiva and Oliveira), University of Sao Paulo, Sao Paulo, Brazil.

The authors declare no conflicts of interest.

**Correspondence:** Debora Souza Sardinha, MSc, RN, Rua Igarapé, 158, Apartamento 1. Bairro Paraíso, Santo André/SP, 09190-680, Brasil. (debora.sardinha@usp.br; debbysardinha@hotmail.com).

DOI: 10.1097/JTN.0000000000000471

others) before and after the trauma. This questionnaire enables family members to indicate behavioral changes quantitatively using a Likert scale.

Recovery from the consequences of TBI is a dynamic, time-dependent process with a relatively long evolution (Bennet et al., 2013; Liew, Johari, Nasser, & Abdullah, 2009; Scholten et al., 2015; Vieira et al., 2018). Researchers have indicated that in contrast to what happens with physical changes, behavioral changes persist for years without a significant tendency to improve and families need professional help to coexist with the personality changes of their relatives even 10–15 years after the trauma (Jennekens, de Casterlé, & Dobbels, 2010; Lippert-Gruner et al., 2006). Besides, the behavioral and cognitive changes after the TBI are considered a greater impediment to reintegration into the society than the physical disabilities (Hora & Sousa, 2005; Kolitz et al., 2003; O'Neill, Gardani, Findlay, Whyte, & Cullen, 2014; Soeda et al., 2005; Tam et al., 2015). In cases of sensory and motor deficiencies, implementing compensation strategies and the availability of equipment could help patients obtain a good quality of life. However, despite advances in care and acute treatment and rehabilitation, cognitive and behavioral changes represent a barrier to the recovery process, social reintegration, and the functional independence of TBI patients (Lippert-Gruner et al., 2006; Saxton, Younan, & Lah, 2013; Soeda et al., 2005).

Among the injuries resulting from TBI, diffuse axonal injury (DAI) is one of the most common injuries after blunt trauma and is present in more than 40% of hospital admissions due to TBI (Meythaler, Peduzzi, Eleftheriou, & Novack, 2001). Clinically, DAI is characterized by a coma episode without focal lesion and is pathologically defined by axonal damage in several regions of the brain parenchyma, causing a rupture in neural connectivity (Su & Bell, 2016). It is considered one of the most important causes of cognitive sequelae and is a determinant of the morbidity and mortality of TBI patients (Meythaler et al., 2001; Solmaz et al., 2017; Su & Bell, 2016; Vieira et al., 2016). In comparison with focal lesions, DAI is more strongly correlated with cognitive and behavioral symptoms, as it mainly affects the frontal lobes of the encephalon that are highly susceptible to these alterations (Schroeter et al., 2007; Soeda et al., 2005). As a consequence, individuals with DAI have more difficulties with a wide variety of neuropsychological tests than those with a focal lesion (Felmingham, Baguley, & Green, 2004).

Despite the importance of knowing information on the patient's recovery after DAI, there are few studies in the literature that address the consequences of DAI as well as its implications on the behavioral issues of patients. On the basis of these findings, this study analyzed the behavioral changes of patients after DAI in the first year after the trauma, according to family information, and

identified factors associated with these changes. The results of this study should contribute to better clinical practices and provide assistance to patients with DAI and their family members to facilitate the reintegration of trauma patients into the society.

## METHODS

This is a prospective cohort study conducted with follow-up assessments at 3, 6, and 12 months after the traumatic event. The study was approved by the Research Ethics Committee, and the participants signed an informed consent form to obtain authorization for inclusion in the research. The data were collected at a university hospital located in Sao Paulo, Brazil. The emergency department of this institution provides care for trauma cases of high complexity and is a referral center for neurosurgery treatment. This hospital is attached to an outpatient service that provides care to several medical specialties, and the participants in this study were linked to the specialized service for the care of DAI patients.

The study sample was nonrandom and composed of all the patients and families who met the eligibility criteria of this investigation. Patients with DAI admitted to the emergency department at the study site from July 2013 to February 2014 were included. The following criteria were considered for DAI diagnosis: the presence of DAI signs in computed tomography (CT) or magnetic resonance imaging or normal CT and clinical evolution consistent with DAI. Patient selection criteria also included ages 18–60 years and a score of 8 or less on the Glasgow Coma Scale at hospital admission.

Cases transferred from other services were excluded from the study, as were cases with a previous diagnosis of TBI, psychiatric illnesses, or incapacitating chronic conditions. Patients who remained in a coma for less than 6 hr after trauma, those with other lesions in the head region (i.e., focal lesions), and spinal cord severity score of 3 or more on the Abbreviated Injury Scale (AIS; Association for the Advancement of Automotive Medicine [AAAM], 2008) were also excluded. Patients with injuries of this severity in the specified body regions present posttraumatic consequences for a long period after the traumatic event (Braine, 2011), which makes it difficult to distinguish the consequences of DAI in the recovery process.

Family members of patients who survived up to 3 months after trauma were invited to participate in this study as informants in assessing behavioral changes after DAI.

The guest family member was a person older than 18 years who lived in the same house as the patient. This family member, as long as he or she consented to participate in the study, was to be the respondent in the three interviews taking place at 3, 6, and 12 months posttrauma.

A questionnaire designed by Frosch et al. (1997) was used to measure behavioral changes. It evaluates the

effects of the patients' behaviors after DAI by the relative's perception before and after the trauma and therefore provides information about the behavioral changes presented. This instrument investigates changes in the behaviors of aggressiveness, anxiety, dependency, depression, egocentricity, impulsivity, inappropriate social behavior, irritability, and memory, as well as the presence of mood swings and temper outbursts. The behaviors of patients are quantitatively described as five values by a Likert scale ranging from 1 to 5. Higher scores are indications of behaviors that affect family members more intensely (Braine, 2011; Hassan, Jamalundin, Raman, Roji, & Fei, 2013; Lippert-Gruner et al., 2006). Family members were interviewed individually. The questions about each behavior were asked separately, thus sequentially investigating how much the patient's behavior affected the family member before the trauma and how much it was affecting the family member at the time of the interview. The difference in the Likert scale score between these two periods characterized the behavioral changes observed in the patient by the family member.

Severity of DAI was measured using the ordinal scale and the Gennarelli (1987) classification, along with the AIS (AAAM, 2008). These publications propose a classification of DAI as mild, moderate, or severe. In mild DAI, the coma lasts for 6–24 hr; in moderate DAI, coma lasts longer than 24 hr but is not accompanied by brainstem signs such as decerebration, decortication, arterial hypertension, hyperthermia, or hyperhidrosis; and in severe DAI, coma lasts longer than 24 hr and brainstem signs are observed.

On data analysis, behavioral changes of the patients were initially categorized as favorable, unfavorable, and absent, considering the behaviors at the evaluation time in comparison with the period before the trauma. Patients who presented concomitant favorable and unfavorable behaviors were also observed. After this analysis, the difference between the scores before and after the trauma in the periods of 3, 6, and 12 months posttrauma was determined for all analyzed cases and behaviors to identify the intensity of the observed behavior changes. Considering that higher scores on the Likert scale of the Frosch et al. (1997) questionnaire indicate behaviors that affect the family more intensely, positive values of this difference indicated that there was improvement and negative values showed worsening in the patient's behavior according to his or her relative. Once the differences were established, the mean and standard deviation values for each behavior at the different evaluation times (3, 6, and 12 months posttrauma) were calculated.

A structure of repeated measures was worked out in the data to identify behavioral changes after DAI in this study, meaning that two information sets were obtained (before and at 3, 6, and 12 months after the trauma) from

the same respondent and therefore of the same patient. Thus, the mixed-effects model was used, being considered more appropriate than repeated measurements (Fausto, Carneiro, Antunes, Pinto, & Colosimo, 2008). In applying this model, the intercept measured whether the averages at 3, 6, and 12 months were equal to zero and the time effect if the means were equal to one another. The mixed-effects model also was used to identify associations between sociodemographic variables (gender, age, occupational situation, monthly family income *per capita*, marital status, and education at the time of trauma), DAI severity, and behavioral changes. First, the interaction effects over time were analyzed for each independent variable for all behaviors separately. Then, the main effects were also analyzed for each variable and behavior, thus generating *p* and *f* values. The R program v.3.4.2 was used for all analyses, and 5% was considered as the level of significance.

## RESULTS

Seventy-one patients were initially selected who met the inclusion criteria of this study. However, 17 patients were excluded because they did not have the continuity of the same family member attending each of the three follow-up evaluations and five more were excluded because the respondent did not live at the same house of the patients at the time of the evaluations. Thus, the total number of patients included was 48. The majority of the patients were male (89.6%), never married or divorced (60.4%), and aged between 18 and 28 years (52.1%), with a mean age of 28.8 years. Regarding education, 43.8% of the sample had received a complete secondary school education, 35.4% only completed elementary education, and 20.8% did not complete elementary education.

The majority of patients (89.6%) were employed before the trauma. The average monthly family income *per capita* was \$428.67; however, it was only \$202.39 in 58.3% of the cases. Regarding DAI severity, the majority of patients had a mild injury (56.3%) and the severity was moderate in 31.3% of the cases. Participants with severe DAI (12.4%) were in the minority. The interviewed family members were mostly female (83.3%) and aged 35–50 years (58.3%), with a mean age of 42.9 years. The mother–father relationship was the most frequent (52.1%), followed by spouse (29.2%) and brother (14.5%).

Behavioral changes after trauma were observed in almost all studied cases: in 95.8% of cases at 3 and 6 months, and in 97.9% of cases at the 12-month period. Table 1 shows that patients' unfavorable behavioral changes were frequent in relation to the period before the trauma, reaching 91.6% of the patients evaluated at 6 months after the DAI. Of these, only 50.0% presented unfavorable behavioral changes and 41.6% presented a mix of favorable and unfavorable behavioral changes.

**TABLE 1 Patients With Diffuse Axonal Injury According to Behavioral Changes in Relation to the Period Before the Injury<sup>a</sup> at 3, 6, and, 12 months After the Trauma**

Behavioral Change	3 Months, <i>n</i> (%)	6 Months, <i>n</i> (%)	12 Months, <i>n</i> (%)
Favorable	7 (14.6)	2 (4.2)	5 (10.4)
Unfavorable	21 (43.7)	24 (50.0)	24 (50.0)
Favorable/unfavorable	18 (37.5)	20 (41.6)	18 (37.5)
Absent	2 (4.2)	2 (4.2)	1 (2.1)
Total	48 (100.0)	48 (100.0)	48 (100.0)

<sup>a</sup>Includes all behaviors assessed in the Frosch et al. (1997) questionnaire.

The relatives reported unfavorable changes in 81.2% of cases at 3 months and in 87.5% of cases at 12 months.

The behaviors that were most frequently reported to have changed favorably were impulsivity (18.7%), irritability, mood swings (16.7%), and temper outbursts (14.6%). Among the unfavorable changes, irritability, memory, and dependency predominated (26 subjects, 54.2% of the sample). The frequencies of individuals with changes related to anxiety (45.8%), depression (39.6%), and mood swings (31.2%) were also highlighted.

The intensity of the behavioral changes indicated by the relatives of the DAI patients was analyzed considering the difference in the Likert scale scores obtained by the Frosch et al. (1997) questionnaire in relation to the periods before and after the trauma. Table 2 shows the means, standard deviations, and *p* values of the Likert scale scores at 3, 6, and 12 months after the trauma. The negative values of the means show that almost all the behaviors presented a tendency to worsen after trauma. As revealed by the mixed-model statistical analysis, there was a statistically significant difference in the means for the results of the 3, 6, and 12-month evaluations only for inappropriate social behavior (*p* = .005). There was an indication that the means were equal for the other behaviors. There was a statistically significant difference in relation to the intercept for anxiety (*p* = .005), dependency (*p* < .0001), depression (*p* = .000), irritability (*p* = .000), and memory (*p* = .003), indicating that the means in these cases were significantly different from zero in at least one of the three performed evaluations.

Figure 1 shows the results presented in Table 2, where it can be observed that the average of the behaviors of aggressiveness, egocentricity, impulsivity, inappropriate social behavior, and temper outbursts was close to the reference line and did not differ from zero according to statistical analyses. In addition, the outlines of most behaviors were below the reference line (zero), indicating unfavorable behavioral change. Considering the results obtained at 3, 6, and 12 months after trauma, the memory behavior was the one that presented the farthest trajectory from the reference line, indicating more intense

worsening in relation to before the trauma when compared with the other behavioral measures. Although inappropriate social behavior did not change significantly in relation to the period before the trauma (*p* = .430), the comparison of means of the three evaluations reached levels of significance (*p* = .005), with a negative mean value at 3 months, slightly positive at 6 months, and very close to zero at 12 months, as observed in Figure 1.

Table 3 describes results of the statistical analysis of the association between sociodemographic variables and behaviors that showed changes in relation to the period prior to the trauma. This table shows significant differences in the family income *per capita* of DAI patients who presented changes in relation to the behavior of depression (*p* = .032) and in the age of those who presented changes in irritability after trauma (*p* = .048).

In the correlation diagram of Figure 2, it can be observed that in relation to depression, the higher the monthly family income *per capita*, the more positive the difference was between the Likert scale scores before and after the trauma. Therefore, there was an indication that the higher the income, the lower the intensity of depression after trauma among the analyzed cases. This is mainly evident in the first 6 months after the trauma, and this relationship is less pronounced at 12 months.

In Figure 3, the correlation diagram shows that older individuals presented a more positive difference between the Likert scale scores before and after the trauma. Thus, the greater the age, the lower the occurrence of irritability after trauma. This association was more evident after the first 6 months of the injury.

Table 4 shows that dependency was the only analyzed behavior that correlated with DAI severity. The more severe the lesion, the greater the dependency of the patient, indicating a more negative difference between the Likert scale scores before and after trauma. Patients with mild and moderate injuries had a very similar evolution and tendency to decrease their dependence over time (between 3 and 12 months after trauma). Severity had a similar level of dependence between the evaluations.

**TABLE 2** Comparison of the Means and Standard Deviations of the Difference in Scores Before and After the Trauma at 3, 6, and 12 Months<sup>a</sup>

Behavioral Reports	<i>M</i>	<i>SD</i>	<i>p</i> <sup>b</sup>	
			Time <sup>c</sup>	Intercept <sup>d</sup>
Aggressiveness				
3 months	−0.29	1.03		
6 months	−0.27	1.23	.857	.096
12 months	−0.21	1.35		
Anxiety				
3 months	−0.71	1.37		
6 months	−0.46	1.44	.269	.005
12 months	−0.40	1.59		
Dependency				
3 months	−1.23	1.36		
6 months	−0.90	1.34	.069	<.0001
12 months	−0.75	1.28		
Depression				
3 months	−0.58	1.16		
6 months	−0.38	0.87	.509	.000
12 months	−0.48	1.20		
Egocentricity				
3 months	0.06	0.84		
6 months	0.04	0.68	.810	.495
12 months	0.10	0.88		
Impulsivity				
3 months	−0.13	1.08		
6 months	−0.19	0.96	.727	.269
12 months	−0.08	0.96		
Inappropriate social behavior				
3 months	−0.31	0.93		
6 months	0.13	0.94	.005	.430
12 months	−0.06	0.93		
Irritability				
3 months	−0.75	1.42		
6 months	−0.75	1.68	.808	.000
12 months	−0.63	1.45		
Memory				
3 months	−1.00	1.25		
6 months	−1.25	1.28	.261	<.0001
12 months	−1.15	1.18		

(continues)



**TABLE 2** Comparison of the Means and Standard Deviations of the Difference in Scores Before and After the Trauma at 3, 6, and 12 Months<sup>a</sup> (Continued)

Behavioral Reports	<i>M</i>	<i>SD</i>	<i>p</i> <sup>b</sup>	
			Time <sup>c</sup>	Intercept <sup>d</sup>
Mood swings				
3 months	−0.42	1.15		
6 months	−0.44	1.18	.938	.003
12 months	−0.48	1.27		
Temper outbursts				
3 months	−0.06	0.93		
6 months	−0.21	1.47	.710	.340
12 months	−0.15	1.30		

<sup>a</sup>Bold values show data that presented significant differences according to statistical analyzes.

<sup>b</sup>Mixed-effects models. Bold values show data that presented significant differences according to statistical analyzes.

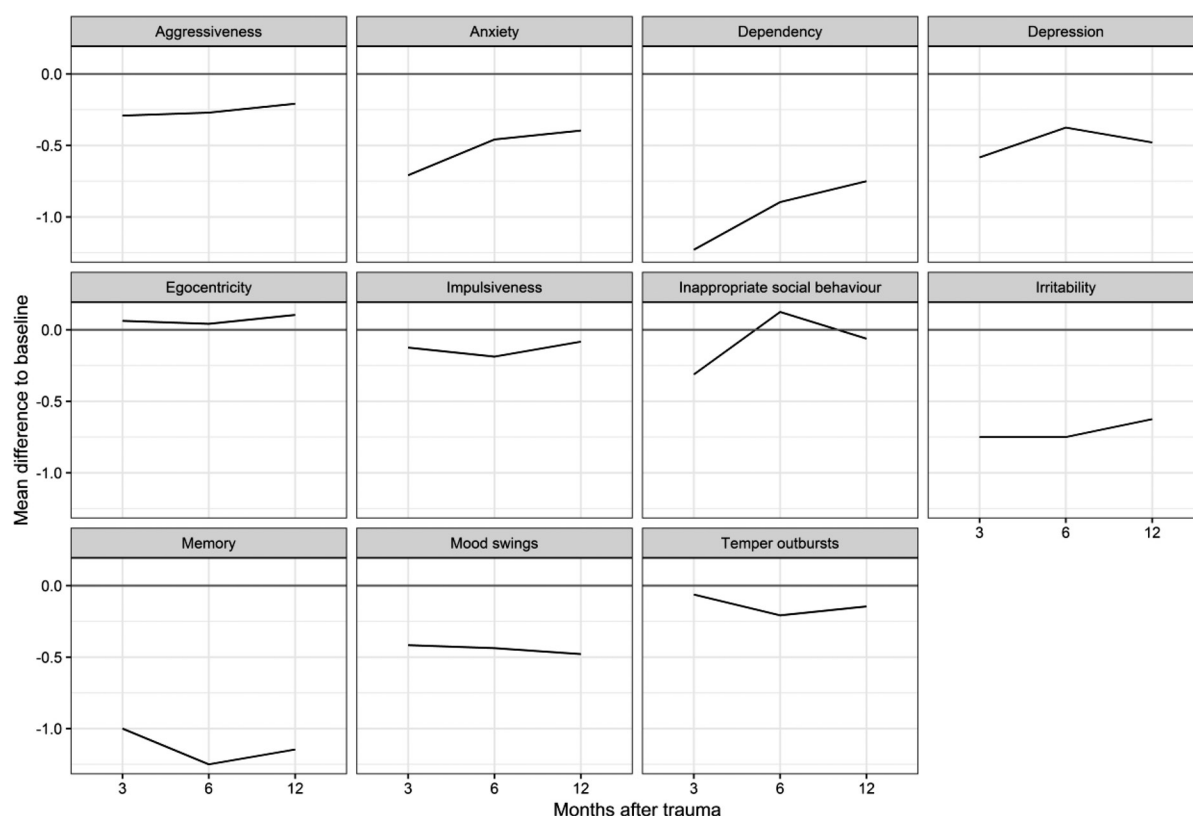
<sup>c</sup>Comparison between the means of 3, 6, and, 12 months posttrauma.

<sup>d</sup>Indication if the means differed statistically from zero.

## DISCUSSION

In this study, the responses of family members to the Frosch et al. (1997) questionnaire indicated a high frequency of

unfavorable behavioral changes after DAI and almost all patients showed these changes at some time after trauma. These results support the assumptions that DAI strongly



**Figure 1.** Evolution of the means for the intensity of changes in the behavior of patients with diffuse axonal injury at 3, 6, and 12 months after trauma.

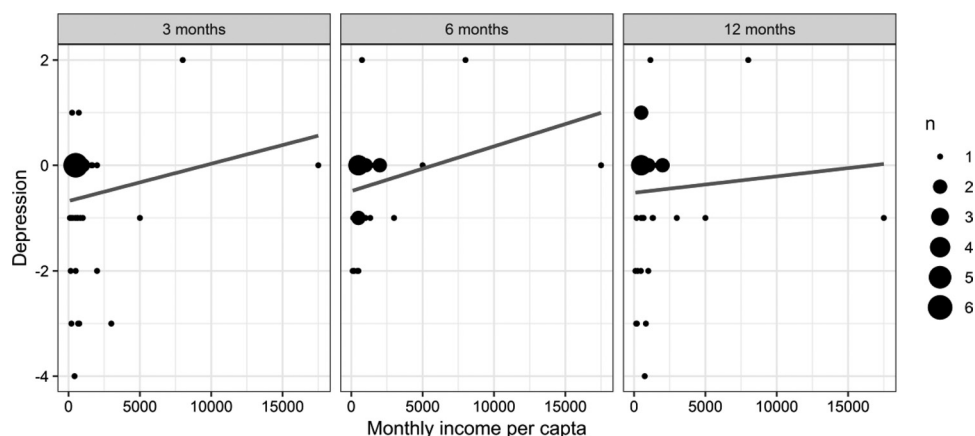
**TABLE 3 Analysis of the Mixed-Effects Model for Behavioral Changes in Relation to the Pretrauma Period and Sociodemographic Characteristics**

Behavioral Reports	Sociodemographic Characteristics	numDF <sup>a</sup>	denDF <sup>b</sup>	<i>F</i>	<i>p</i> <sup>c</sup>
Anxiety	Sex	1	36	1.330528	.256
	Age	1	36	0.308351	.582
	Education	1	36	0.234922	.631
	Marital status	2	36	3.038739	.060
	Employment status	2	36	0.266158	.768
	Monthly family income <i>per capita</i>	1	36	0.683428	.414
Dependency	Sex	1	36	0.011452	.915
	Age	1	36	0.316749	.577
	Education	1	36	0.017175	.897
	Marital status	2	36	1.194964	.314
	Employment status	2	36	0.271511	.764
	Monthly family income <i>per capita</i>	1	36	1.337504	.255
Depression	Sex	1	36	0.00143	.970
	Age	1	36	0.987553	.327
	Education	1	36	2.150719	.151
	Marital status	2	36	0.686178	.510
	Employment status	2	36	0.690731	.508
	Monthly family income <i>per capita</i>	1	36	4.988827	.032
Irritability	Sex	1	36	0.227963	.636
	Age	1	36	4.177904	.048
	Education	1	36	1.092854	.303
	Marital status	2	36	1.199703	.313
	Employment status	2	36	0.462969	.633
	Monthly family income <i>per capita</i>	1	36	0.521606	.475
Memory	Sex	1	36	0.147481	.703
	Age	1	36	0.052514	.820
	Education	1	36	0.001557	.969
	Marital status	2	36	0.288082	.751
	Employment status	2	36	0.231067	.795
	Monthly family income <i>per capita</i>	1	36	0.418299	.522
Mood swings	Sex	1	36	0.275873	.603
	Age	1	36	1.003202	.323
	Education	1	36	0.515167	.478
	Marital status	2	36	0.268285	.766
	Employment status	2	36	0.197761	.822
	Monthly family income <i>per capita</i>	1	36	0.566012	.457

<sup>a</sup>Degrees of freedom in the numerator of the *F*-statistic.

<sup>b</sup>Degrees of freedom in the denominator of the *F*-statistic.

<sup>c</sup>Mixed-effects model.



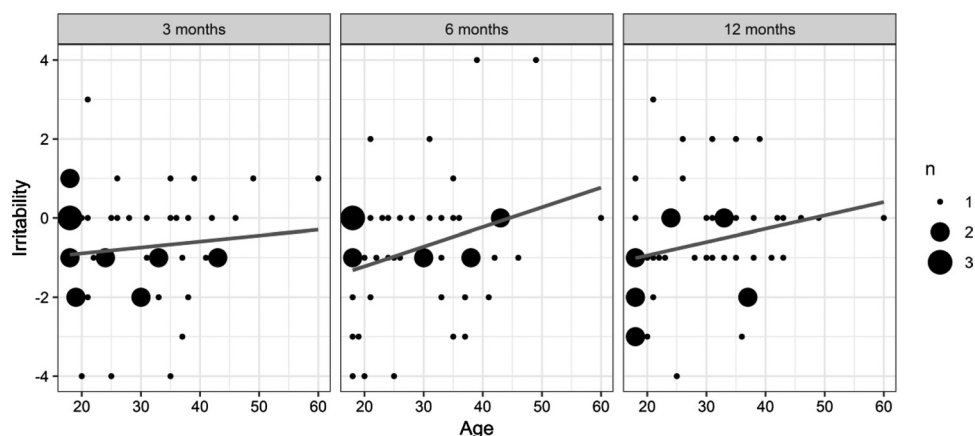
**Figure 2.** Correlation diagram between depression after trauma and monthly family income *per capita* of patients at 3, 6, and 12 months after diffuse axonal injury.

correlates with cognitive and behavioral symptoms when compared with focal lesions and are similar to the results of German and Sweden researchers that show a marked presence of cognitive, mental, and psychomotor dysfunctions after DAI. In a German investigation that evaluated 10 patients with DAI who presented severe TBI and underwent neuropsychiatric evaluation, it was observed that all had deficiency in performance in at least one of the tests of the applied inventory to identify behavioral changes (Schroeter et al., 2007). Moreover, in a study conducted in Sweden, the evaluation of cognitive functions of patients with indications of DAI revealed that all had this type of dysfunction even 1 year after injury (Esbjörnsson et al., 2013). According to the authors of the last study, cognitive, mental, and psychomotor dysfunctions in DAI are common, which can cause short- and long-term disabilities, as well as lead to death in cases with more serious pathological damage (Esbjörnsson et al., 2013).

In the present investigation, the most frequent adverse behavioral changes were irritability, memory, and

dependency (54.2%), followed by anxiety (45.8%), depression (39.6%), and mood swings (31.2%). These six types of behaviors also stood out among the others because they presented mean values of the Likert scale scores before and after DAI that were significantly different from zero, according to the mixed-effects model analysis, suggesting that there was a change in these behaviors after trauma. Among the behaviors that were indicated as significantly modified after injury in the current investigation, memory presented the most intense worsening because it had the most negative mean score difference on the Likert scale (between  $-1$  and  $-1.25$ ). Other authors (Esbjörnsson et al., 2013) have also pointed out that memory impairment is the most common impairment in DAI and it hinders the return to work within the first year after trauma.

Few studies have analyzed behavioral changes in DAI patients. However, results of TBI studies support the findings of the current research. An Australian study that followed TBI patients at a rehabilitation clinic reports that 60% of respondents reported memory problems, more



**Figure 3.** Correlation diagram between changes in irritability after trauma and age of the patients at 3, 6, and 12 months after diffuse axonal injury.



**TABLE 4** Analysis of the Mixed-Effects Model for Behavioral Changes in Relation to the Pretrauma Period and Diffuse Axonal Injury Severity<sup>a</sup>

Behavioral Reports	<i>F</i>	numDF <sup>b</sup>	denDF <sup>c</sup>	<i>p</i> <sup>d</sup>
Anxiety	0.032752	2	36	.968
Dependency	5.389207	2	36	<b>.009</b>
Depression	0.819762	2	36	.449
Irritability	0.035013	2	36	.966
Memory	0.455593	2	36	.638
Mood swings	0.206448	2	36	.814

<sup>a</sup>Bold values show data that presented significant differences according to statistical analyzes.

<sup>b</sup>Degrees of freedom in the numerator of the *F*-statistic.

<sup>c</sup>Degrees of freedom in the denominator of the *F*-statistic.

<sup>d</sup>Mixed-effects model.

than two thirds cited increased irritability, and nearly half of the sample found themselves more anxious and depressed after the trauma (Ponsford et al., 2014). Another study that analyzed the results of patients with brain trauma reported by relatives showed that irritability was a problem in 63% of the cases at 3 months after the trauma, anxiety and depression were present in more than half of the evaluated patients, memory problems were observed in 73% of the sample, and mood swings were observed in 33% of the sample (McKinlay, Brooks, Bond, Martinage, & Marshall, 1981). A study conducted in the same hospital of this study in 2001 that also applied the Frosch et al. (1997) questionnaire in interviews with relatives of TBI patients, on average 4.42 years after a traumatic event, showed that the behaviors of memory, dependency, anxiety, irritability, depression, and aggressiveness showed the most intense changes after the trauma (Hora & Sousa, 2005).

Studies conducted on DAI and TBI patients show that they display a tendency to ameliorate their emotional and behavioral disorders over time, but there are cases in which these disorders become chronic and limiting (Arciniegas & Wortzel, 2014; Johnson, Stewart, & Smith, 2013; Lippert-Gruner et al., 2006; Su & Bell, 2016). In the present study, the analysis of the evolution of behavior changes showed that they maintained the same change intensity between 3 and 12 months after the traumatic event, indicating no improvement during this period. This result is supported by recent evidence that suggests that axonal degeneration continues years after TBI and appears to play an important role in the development of cognitive impairment syndromes such as Alzheimer's disease (Johnson et al., 2013). Although pathological

changes in axons can manifest in the immediate loss of consciousness after DAI and cognitive dysfunctions that characterize the TBI, the different continuity forms of axonal pathology over time have not yet been established (Johnson et al., 2013; Su & Bell, 2016).

In using highly sensitive markers for DAI, researchers have observed increased axonal pathology with a peak within the first 24 hr after injury, followed by leveling out. Although the 24-hr period appears to represent the peak of brain damage, axonal damage has been observed at weeks and months posttrauma and, in a small number of cases, even years after TBI, perhaps indicating persistent degeneration of the white matter in a percentage of cases. Furthermore, there is evidence of selective loss of white matter after trauma, thus supporting this assumption (Johnson et al., 2013). On the contrary, according to research that seeks to understand the pathological histology of DAI and the acute and chronic pathogenesis that accompanies TBI, there can be many other subtle pathological changes in DAI that affect functional outcomes such as changes in dendrites, imbalances in neurotransmitters, or changes in the cerebral metabolism. These considerations make DAI a complex process that begins with stretching and disruption of axons, eventually becoming a syndrome of cerebral disconnection and impairment in function in the long term (Johnson et al., 2013; Su & Bell, 2016).

Inappropriate social behavior was a behavior that did not present significant alteration after trauma in relation to the previous period. Few patients had this behavioral change; however, it was the only behavior that showed a significant change between 3 and 12 months after DAI. There was an unfavorable alteration at 3 months that evolved into a similar situation to the period before the trauma at 6 and 12 months. These findings may be related to states of mental confusion following coma periods after the trauma (American Psychiatric Association, 2015; Gouveia et al., 2009).

Although most studies focused on the negative aspects resulting from trauma, qualitative research aimed at caregivers of DAI patients pointed out that some positive results also occur following this injury. According to the authors, the results appear to be mediated by factors that interact and can bring benefits, including adaptations in family functionality, resilience, coping mechanisms, community support, information empowerment, favorable financial condition, spirituality/religiosity, and psychological adjustment (Syed, Jamaludin, Abd, Mohd, & Wan, 2013). Importantly, the trauma experience is often related to the threat of death, which can trigger a resignification of life and its relationships to the individual.

The statistical analysis identified income *per capita*, age, and severity of the injury as factors associated with behavioral changes after DAI. It was observed that the higher the family income *per capita*, the lower the

depression levels of the patients. Favorable financial condition is a factor that can benefit recovery after DAI, according to a previous study (Syed et al., 2013). In Brazil, a cross-sectional population-based study (Boing et al., 2012) identified that the prevalence of depression was higher in economically disadvantaged people. In the group of individuals with incomes up to \$152.98, depression was present in 18.1% of the cases, whereas the group with an income greater than \$350.81 had a lower percentage of depression cases (13.6%). Furthermore, the insufficient health supplies for the Brazilian population in the public system make economically favored people to have greater access to specialized professionals and differentiated treatments, which leads to an improved ability to cope with the consequences of trauma.

Another finding of the present study was that the greater the age, the lower the intensity of changes related to irritability. Regarding this finding, it is worth noting that age extremes were not included in the sample of this study, and the results indicated that young adult individuals tended to present more intense worsening in irritability behavior than middle-aged patients. In a publication about the conception of middle age in the aging process, the authors pointed out that there are physical limitations and losses in aesthetics in the middle age, but there lies the counterpoint of maturation that brings more security, wisdom, and tranquility (Antunes & Silva, 2013).

It was also observed that the more severe the DAI, the greater the dependence of the patient. A study that evaluated DAI patients and risk factors associated with unfavorable outcomes 6 months after trauma (Vieira et al., 2016) showed that patients with severe injury were in the group of people who were dependent on a caregiver whereas patients with mild and moderate DAI were almost entirely independent.

Among the limitations of the current research, it is worth highlighting the selection of patients from only one reference institution for trauma treatment, which may restrict generalizing the results. Although the Frosch et al. (1997) questionnaire has been previously used to study survivor and caregivers after TBI, the questionnaire is not validated and its application presupposes that the evaluation of behavioral changes of the patients is based on the family's point of view. Despite the mentioned limitations, this study brought contributions to the knowledge about behavioral change specificities (frequency, intensity, type, and associated factors) observed in DAI patients and about their clinical evolution 1 year after the trauma. The few articles in the current literature about the subject of this study focus on just some points of the behavioral changes after DAI; thus, the most relevant differential of this investigation was to present an overview of the topic on its results.

Importantly, in the current study, the changes in the behavior seen as unfavorable by family members of

the patients were observed in almost the entire sample, indicating that these consequences of trauma may be inherent in DAI. Thus, understanding the behavioral change specificities after DAI can aid health professionals to identify their influence on the reintegration of DAI patients into the society and refer a great number of TBI patients to appropriate treatment. The results of this study also showed the importance of providing long-term support to people with DAI, as well as to the family caregivers to cope with the new health condition of their relatives. Finally, little is known about the consequences of DAI, but there are indications that neuropsychological disorders are the most relevant issue for these patients. In consequence, future research is needed with a focus on changes in behavior, showing their relation to pathological changes. The need for studies on interventions to improve treatment and rehabilitation of these patients is great.

## CONCLUSION

Unfavorable changes in behavior were reported by family members in the majority of DAI patients. Favorable changes in behavior were less frequently observed and generally occurred in patients who indicated improvement in some behaviors and worsening in others. Irritability, memory alterations, dependency, anxiety, depression, and mood swings were reported after the trauma that lasted up to 12 months after injury. Factors associated with behavioral changes after trauma were monthly family income *per capita*, age, and DAI severity. It was observed that the higher the family income *per capita*, the lower the tendency of the patients to suffer from depression after the injury, and older individuals had less change in irritability after the trauma than younger ones. Patients with more severe DAI became more dependent after the trauma.

## Acknowledgments

This study was financed in part by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*, Brazil (CAPES), Finance Code 001, State of São Paulo Research Foundation (FAPESP) (Process No. 2013/21804-0), and *Conselho Nacional de Desenvolvimento Científico e Tecnológico Universal MCTI- CNPq* (Process No. 444855/214-9).

## KEY POINTS

- Unfavorable behavioral changes are common in DAI patients and do not lessen over time.
- Lower income patients have a greater risk of depression after DAI, and younger patients present with greater irritability after DAI.
- Severity of DAI was not related to behavioral changes, except when the dependency behavior was analyzed.

## REFERENCES

- American Psychiatric Association. (2015). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed.). Porto Alegre, Rio Grande do Sul, Brazil: Artmed.
- Antunes, P., & Silva, A. M. (2013). Elementos sobre a concepção de Meia-idade no processo de envelhecimento [Elements about the middle age conception, in the human aging process]. *Kairós Gerontologia*, 16, 123–140.
- Arciniegas, D. B., & Wortzel, H. S. (2014). Emotional and behavioral dyscontrol after traumatic brain injury. *Psychiatric Clinics of North America*, 37, 31–53. doi:10.1016/j.psc.2013.12.001
- Association for the Advancement of Automotive Medicine (AAAM). (2008). *The Abbreviated Injury Scale (AIS): 2005, update 2008*. Des Plaines, IL: Author.
- Bennet, L., Van Den Heuvel, L., Dean, J. M., Drury, P., Wassink, G., & Gunn, A. J. (2013). Neural plasticity and the Kennard principle: Does it work for the preterm brain? *Clinical and Experimental Pharmacology and Physiology*, 40, 774–784. doi:10.1111/1440-1681.12135
- Boing, A. F., Melo, G. R., Boing, A. C., Moretti-Pires, R. O., Peres, K. G., & Peres, M. A. (2012). Association between depression and chronic diseases: Results from a population-based study. *Revista de Saúde Pública*, 46, 617–623.
- Braine, M. E. (2011). The experience of living with a family member with challenging behavior post acquired brain injury. *Journal of Neuroscience Nursing*, 43, 156–164. doi:10.1097/JNN.0b013e3182135bb2
- Esbjörnsson, E., Skoglund, T., Mitsis, M. K., Hofgren, C., Larsson, J., & Sunnerhagen, K. S. (2013). Cognitive impact of traumatic axonal injury (TAI) and return to work. *Brain Injury*, 27, 521–528. doi:10.3109/02699052.2012.743179.
- Esbjörnsson, E., Skoglund, T., & Sunnerhagen, K. S. (2013). Fatigue, psychosocial adaptation and quality of life one year after traumatic brain injury and suspected traumatic axonal injury; Evaluations of patients and relatives: A pilot study. *Journal of Rehabilitation Medicine*, 45, 771–777. doi:10.2340/16501977-1170
- Fausto, M. A., Carneiro, M., Antunes, C. M., Pinto, J. Á., & Colosimo, E. A. (2008). O modelo de regressão linear misto para dados longitudinais: uma aplicação na análise de dados antropométricos desbalanceados [Mixed linear regression model for longitudinal data: Application to an unbalanced anthropometric data set]. *Cadernos de Saúde Pública*, 24, 513–524.
- Felmington, K. L., Baguley, I. J., & Green, A. M. (2004). Effects of diffuse axonal injury on speed of information processing following severe traumatic brain injury. *Neuropsychology*, 18, 564–571.
- Frosch, S., Gruber, A., Jones, C., Myers, S., Noel, E., & Westerlund, A. (1997). The long term effect of traumatic brain injury on the roles of caregivers. *Brain Injury*, 11, 891–906.
- Gennarelli, T. A. (1987). *Cerebral concussion and diffuse brain injuries*. In P. R. & Cooper (Ed.), *Head injury* (2nd ed., pp. 108–124). Baltimore, MD: Williams & Wilkins.
- Gouveia, P. A. R., Prade, C. V., Lacerda, S. S., Boschetti, W. L., & Andreoli, P. B. A. (2009). Reabilitação neuropsicológica em fase aguda e crônica após Traumatismo Crânio- Encefálico (TCE) grave: relato de caso [Neuropsychological rehabilitation during acute and chronic stages in severe traumatic brain injury (TBI): Case report]. *Contextos Clínicos*, 2, 18–26.
- Hassan, S. T. S., Jamaluddin, H., Raman, R. A., Roji, H. M., & Fei, W. F. (2013). Mental trauma experienced by caregivers of patients with diffuse axonal injury or severe traumatic brain injury. *Trauma Monthly*, 18, 56–61. doi:10.5812/traumamon.11522
- Hora, E. C., & Sousa, R. M. C. (2005). Os efeitos das alterações comportamentais das vítimas de trauma crânio-encefálico para o cuidador familiar [Effect of the behavioral alterations of victims of traumatic brain injury for the family caregiver]. *Revista Latino Americana de Enfermagem*, 13, 93–98.
- Hora, E. C., & Sousa, R. M. C. (2009). Adaptação transcultural do instrumento family needs questionnaire [Cross-cultural adaptation of the instrument “Family Needs Questionnaire”]. *Revista Latino Americana de Enfermagem*, 17, 541–547.
- Jennekens, N., de Casterlé, B. D., & Dobbels, F. (2010). A systematic review of care needs of people with traumatic brain injury (TBI) on a cognitive, emotional and behavioral level. *Journal of Clinical Nursing*, 19, 1198–1206. doi:10.1111/j.1365-2702.2009.03114.x
- Johnson, V. E., Stewart, W., & Smith, D. H. (2013). Axonal pathology in traumatic brain injury. *Experimental Neurology*, 246, 35–43. doi:10.1016/j.expneurol.2012.01.013
- Kolitz, B. P., Vanderploeg, R. D., & Curtiss, G. (2003). Development of the key behaviors change inventory: A traumatic brain injury behavioral outcome assessment instrument. *Archives of Physical Medicine and Rehabilitation*, 84, 277–284.
- Liew, B. S., Johari, S. A., Nasser, A. W., & Abdullah, J. (2009). Severe traumatic brain injury: Outcome in patients with diffuse axonal injury managed conservatively in hospital Sultanah Aminah, Johor Bahru—An observational study. *The Medical Journal of Malaysia*, 64, 280–288.
- Lippert-Gruner, M., Kuchta, J., Hellmich, M., & Klug, N. (2006). Neurobehavioral deficits after severe traumatic brain injury (TBI). *Brain Injury*, 20, 569–574.
- McKinlay, W. W., Brooks, D. N., Bond, M. R., Martinage, D. P., & Marshall, M. M. (1981). The short-term outcome of severe blunt head injury as reported by relatives of the injured persons. *Journal of Neurology, Neurosurgery & Psychiatry*, 44, 527–533.
- Meythaler, J. M., Peduzzi, J. D., Eleftheriou, E., & Novack, T. A. (2001). Current concepts: Diffuse axonal injury-associated traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, 82, 1461–1471.
- O'Neill, B., Gardani, M., Findlay, G., Whyte, T., & Cullen, T. (2014). Challenging behavior and sleep cycle disorder following brain injury: A preliminary response to agomelatine treatment. *Brain Injury*, 28, 378–381. doi:10.3109/02699052.2013.865264
- Ponsford, J. L., Downing, M. G., Olver, J., Ponsford, M., Acher, R., Carty, M., & Spitz, G. (2014). Longitudinal follow-up of patients with traumatic brain injury: Outcome at two, five, and ten years post-injury. *Journal of Neurotrauma*, 31, 64–77. doi:10.1089/neu.2013.2997
- Saxton, M. E., Younan, S. S., & Lah, S. (2013). Social behavior following severe traumatic brain injury: Contribution of emotion perception deficits. *NeuroRehabilitation*, 33, 263–271. doi:10.3233/NRE-130954
- Scholten, A. C., Haagsma, J. A., Andriessen, T. M., Vos, P. E., Steyerberg, E. W., van Beeck, E. F., & Polinder, S. (2015). Health-related quality of life after mild, moderate and severe traumatic brain injury: Patterns and predictors of suboptimal functioning during the first year after injury. *Injury*, 46, 616–624. doi:10.1016/j.injury.2014.10.064
- Schroeter, M. L., Ettrich, B., Schwier, C., Scheid, R., Guthke, T., & von Cramon, D. Y. (2007). Diffuse axonal injury due to traumatic brain injury alters inhibition of imitative response tendencies. *Neuropsychologia*, 45, 3149–3156.
- Soeda, A., Nakashima, T. N., Okumura, A., Kuwata, K., Shinoda, J., & Iwama, T. (2005). Cognitive impairment after traumatic brain injury: A functional magnetic resonance imaging study using the Stroop task. *Neuroradiology*, 47, 502–506.
- Solmaz, B., Tunc, B., Parker, D., Whyte, J., Hart, T., Rabinowitz, A., ... Verma, R. (2017). Assessing connectivity related injury burden in diffuse traumatic brain injury. *Human Brain Mapping*, 38, 2913–2922. doi:10.1002/hbm.23561
- Su, E., & Bell, M. (2016). Diffuse axonal injury. In D. Laskowitz & G. Grant, (Eds.), *Translational research in traumatic brain*

- injury* (Chapter 3). Boca Raton, FL: CRC Press/Taylor & Francis. Retrieved from <https://www.ncbi.nlm.nih.gov/books/NBK326722>
- Syed, H. S. T., Jamaludin, H., Abd, R. R., Mohd, R. H., & Wan, F. K. (2013). Mental trauma experienced by caregivers of patients with diffuse axonal injury or severe traumatic brain injury. *Trauma Monthly*, 18, 56–61. doi:10.5812/traumamon.11522
- Tam, S., McKay, A., Sloan, S., & Ponsford, J. (2015). The experience of challenging behaviours following severe TBI: A family perspective. *Brain Injury*, 29(7–8), 813–821. doi:10.3109/02699052.2015.1005134
- Vieira, R. C. A., Paiva, W. S., de Oliveira, D. V., Guirado, V. M. P., Lança, E. F. C., & Sousa, R. M. C. (2018). Recovery of patients with pure diffuse axonal injury who remained in a coma for 6 hours or more. *World Neurosurgery*, 109, 140–146. doi:10.1016/j.wneu.2017.09.101
- Vieira, R. C. A., Paiva, W. S., de Oliveira, D. V., Teixeira, M. J., de Andrade, A. F., & Sousa, R. M. (2016). Diffuse axonal injury: Epidemiology, outcome and associated risk factors. *Frontiers in Neurology*, 7, 178.