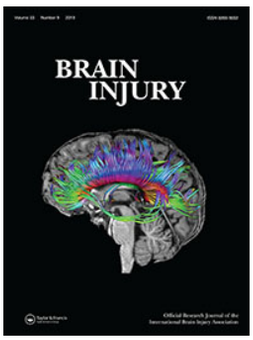

Brain Injury

ISSN: 0269-9052 (Print) 1362-301X (Online) Journal homepage: https://www.tandfonline.com/loi/ibij20

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To cite this article: U. Bivona, A. Costa, M. Contrada, D. Silvestro, E. Azicnuda, M. Aloisi, G. Catania, P. Ciurli, C. Guariglia, C. Caltagirone, R. Formisanohttps://orcid.org/0000-0002-2516-0540 & G.P. Prigatano (2019) Depression, apathy and impaired self-awareness following severe traumatic brain injury: a preliminary investigation, Brain Injury, 33:9, 1245-1256, DOI: 10.1080/02699052.2019.1641225

To link to this article: https://doi.org/10.1080/02699052.2019.1641225

BRAIN INJURY
2019, VOL. 33, NO. 9, 1245–1256
https://doi.org/10.1080/02699052.2019.1641225

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Depression, apathy and impaired self-awareness following severe traumatic brain injury: a preliminary investigation

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ABSTRACT

Primary Objective: The primary aim of this study was to determine the frequency of severe impaired self-awareness (ISA) in patients with severe traumatic brain injury (TBI) and the correlates of selected clinical, neuropsychiatric and cognitive variables. The secondary aim of the study was to assess depression and apathy on the basis of their level of self-awareness.

Methods: Thirty patients with severe TBI and 30 demographically matched healthy control subjects (HCs) were compared on measures of ISA, depression, anxiety, alexithymia, neuropsychiatric symptoms and cognitive flexibility.

Results: Twenty percent of the patients demonstrated severe ISA. Severe post-acute ISA was associated with more severe cognitive inflexibility, despite the absence of differences in TBI severity, as evidenced by a Glasgow Coma Scale (GCS) score lower than 9 in all cases in the acute phase. Patients with severe ISA showed lower levels of depression and anxiety but tended to show more apathy and to have greater difficulty describing their emotional state than patients with severe TBI who showed minimal or no disturbance in self-awareness.

Conclusion: These findings support the general hypothesis that severe ISA following severe TBI is typically not associated with depression and anxiety, but rather with apathy and cognitive inflexibility.

ARTICLE HISTORY
Received 28 January 2019
Revised 5 June 2019
Accepted 4 July 2019

KEYWORDS
Severe traumatic brain injury; mood disorders; apathy; self-awareness; neuropsychological rehabilitation

Introduction

Severe traumatic brain injury (TBI) can produce a wide range of neuropsychiatric and neuropsychological disturbances (1–10). The emotional or mood disturbances observed after severe TBI can be a direct result of brain damage or a psychological reaction to the physical and cognitive changes produced by the severe TBI (11,12). They include depression, anxiety, angry outbursts, disinhibition, apathy and alexithymia (13–16). Besides these emotional or mood disturbances, an equally wide range of cognitive disturbances have been reported in this patient group. These include attention and memory impairments, reduced problem-solving abilities and slow speed of information processing (17–20), and executive dysfunctioning (21–24).

Another relevant factor is self-awareness, i.e., the ability to be aware of one's own thoughts, feelings and mental states (25). Important impairments of self-awareness (ISA) of deficits after TBI can involve many different functions, including motor, social judgment, behavioral and overall level of functional competency in everyday life (26–30), and can lead to worse functional outcome (27,31–35). However, despite the high incidence of ISA after severe TBI, it is still difficult to adequately assess them. This is because ISA are actually disturbances of subjective experience and therefore are always measured indirectly (36). Judging the severity of the ISA can be problematic and is often inferred by comparing the patient's subjective reports of their functional capacities with the reports of reliable relatives.

Prigatano and Johnson (37) hypothesized a possible relationship between ISA and disturbances of consciousness (DoC). According to these authors, three vectors [concerning the sleep-wake cycle (Vector 1), the emergence of self-awareness (Vector 2), and the ability to enter the phenomenological field of another person and sense what he/she is experiencing (i.e., Theory of Mind) (Vector 3)] interact and overlap, and ISA after TBI may be a residual form of DoC even if the patient has recovered from coma (37). However, no studies to date have verified this hypothesis.

Heilman and Harciarek (38) noted that even when patients appear to verbally acknowledge their impaired motor abilities, they might demonstrate "diminished concern of the illness or disability." (pg. 89). Babinski introduced the term "anosodiaphoria" to describe this clinical condition (39). Notoriously, patients who show anosodiaphoria are unconcerned with (or tend to minimize) the extent of their deficits (40). It is argued that anosodiaphoria "results from the failure of the error recognition system mediated via anterior cingulate cortex to concurrently activate sympathetic effects in the insula that are necessary for the subjective feeling of emotional distress" (41). Although this term is seldom used today, the phenomenon that Babinski was most likely referring to is now often called "apathy" (42–44). While apathy may have several underlying components (45,46), a loss of desire to pursue activities that

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previously held interest for the person and a loss of emotional reactivity (including indifference or unconcern) over recognized impairments are common features of this condition.

There has been an increase in the literature on apathy after severe TBI (46–48). Measures of apathy have been linked to disturbances of working memory and to other aspects of executive functions (47,49,50). A previous study (51) also found an association between low autonomic reactivity in apathetic patients with severe TBI and reduced self-awareness. In this regard, an interesting observation of Worthington and Wood (46) is that the rates of reported apathy in persons with a history of TBI vary depending on who is asked to report symptoms of apathy. They noted that when patients themselves are asked to describe their own behavior, the incidence of apathy is typically lower than when relatives or significant others are asked about which of the patient's characteristics reflect apathy (46). However, although clinically this often appears to be the case (11), the relationship between apathy and ISA in patients with severe TBI has not been adequately investigated.

Moreover, if apathy is particularly related to ISA (46,51) and to cognitive inflexibility (47,49,50), one should also expect that patients with TBI who show apathy and ISA will perform worse on measures of cognitive flexibility. In fact, the relationship between ISA and cognitive flexibility is still controversial. For example, according to some authors (52,53), the executive system and metacognitive awareness can be considered as processes that have a common role in determining higher order control over "lower" aspects of cognition. In line with this concept, many studies found a close relationship between worse performance on cognitive flexibility tasks and lower levels of self-awareness after severe TBI (5,7,54–58). However, some other studies showed divergent results (59,60); therefore, further investigations are needed to better clarify this issue.

Another relevant issue concerns the relationship between apathy and depression. Although in both cases individuals may show a lack of interest in activities that were previously pleasurable, they are substantially different (61) and mainly related to different kinds of brain damage, such as right frontal lobe dysfunction in the case of apathy (51,62) and left hemisphere dysfunction in the case of depression (62–64), even if the issue regarding brain dysfunction laterality is still being debated (46,65). Furthermore, as apathy is a disorder of *motivation* it should be distinguished from disorders of *mood* such as depression (46). The patient suffering from apathy often does not report feelings of sadness or hopelessness. Rather, these patients are simply indifferent in their emotional reactions. Thus, to specifically assess the potential relationship between apathy and ISA in patients with TBI, the potential effects of depression must also be considered. When depression has been linked to ISA in patients with TBI, it has been typically noted that patients who underestimate their abilities (not impairments or disabilities) show higher levels of depression (66,67). Thus, it is common to find a negative correlation or relationship between severity of ISA and severity of depression. By contrast, in line with other studies (46,51), a positive correlation is assumed to exist between severity of ISA and apathy.

Aims

In light of these observations, the first goal of the present study was to determine the frequency of severe ISA in a sample of patients with a history of severe TBI, and the correlates of selected *clinical, neuropsychiatric* and *cognitive* variables. We expected that patients with severe ISA, compared to those with low ISA, would evidence more severe clinical and neuropsychiatric features and have greater difficulty in performing cognitive tasks.

The second goal of this study was to assess the degree of depression and apathy in patients with severe TBI who showed severe ISA versus no or minimal ISA. We predicted that patients with severe ISA would have less depression but more apathy than patients with no or low ISA. Moreover, we predicted that the level of apathy in patients with TBI would be positively associated with measures of cognitive flexibility, as demonstrated by other authors (47,49,50). By contrast, we expected that the level of depression in patients with TBI would not show a significant association with cognitive inflexibility because it has been shown that level of depression is not related to severity of TBI (68). As depression is often associated with anxiety (69–77) and some depressed patients show alexithymia (56–58), we also investigated these features of patients' emotional functioning.

Methods

Participants

We included 31 patients with severe TBI who had been consecutively admitted to the Post-Coma Unit of Santa Lucia Foundation in Rome (Italy) from November 2010 to October 2012. The study was approved by the local Ethics Committee and all participants or their legal surrogates were included in the study after providing their informed consent.

Participants affected by TBI were recruited according to the following *inclusion* criteria: 1) age ≥ 16 years; 2) diagnosis of severe TBI [Glasgow Coma Scale (GCS) score ≤ 8 in the acute phase]; 3) LCF score ≥ 7; 4) post-traumatic amnesia (PTA) resolution; 5) capacity to undergo formal psychometric evaluation despite cognitive and sensory-motor deficits; 6) time interval from consciousness recovery at least 6 months; 7) availability of informed consent. *Exclusion* criteria for patients recruited in this study were: 1) a history of drug and alcohol addiction; 2) psychiatric diseases; 3) repeated TBI and/or other neurological disorders. After enrolment, one patient was excluded because he was unable to complete the interview due to fatigue.

Thus, the final sample consisted of 30 patients with severe TBI (22 males and 8 females, with a mean age of 31.07 years – SD = 13,53), and a mean educational level of 13,1 years (DS = 3,23).

To evaluate patients' level of self-awareness, according to the discrepancy between their report and that of the caregivers, 30 first-degree relatives (all at least 18 years old) were enrolled: 20 (66.7%) were parents of the patients (15 mothers and 5 fathers), 5 (16.7%) were partners (4 wives and 1 husband), 1 (3.3%) was a son, 3 (10%) were sisters and 1 (3.3%) was an uncle. Only first-

degree relatives who were living with the patients or at least had daily contact with them were enrolled.

Finally, a control group of 30 healthy age/gender/educational level matched control subjects (HCs) were enrolled; both HCs' age and educational level matched those of the patients within ± 2 years.

Exclusion criteria for HCs were: a) a history of drug and alcohol addiction, and b) psychiatric or neurological diseases. All HCs were volunteers who were recruited in our Institute and were included in the study after signing an informed consent form.

Measures

Disturbance of consciousness assessment

The length of DoC was obtained from the patients' medical records.

Functional assessment

A functional assessment was made by a neurologist who adopted the following commonly used scales in the field of acquired brain injury (ABI): the Levels of Cognitive Functioning (LCF) (78), the Disability Rating Scale (DRS) (79) and the Glasgow Outcome Scale (GOS) (80). The LCF ranges from 1 (No Response) to 8 ("Purposeful/Appropriate Response"). In particular, an LCF score of at least 7 (corresponding to "Automatic/Appropriate Response") has been used as one of the inclusion criteria. The DRS and GOS Scales were, instead, used to describe the patients'level of disability (see Table 1, below). In particular, the GOS can range from 1 ("Death") to 5 ("Low disability"). In comparison to the GOS, the DRS addresses many of the shortcomings of the GOS; indeed, the first three items ("Eye Opening," "Communication Ability" and "Motor Response") allow rating *impairment*; cognitive ability for "Feeding", "Toileting" and "Grooming" allow rating *disability*; finally, the "Level of Functioning" and "Employability" items allow rating *handicap*. Higher DRS scores correspond to higher levels of disability; the maximum score a patient can obtain is 29 (Extreme Vegetative State).

Cognitive assessment

To investigate the possible relationship between some executive subcomponents (i.e., cognitive flexibility) (81) of patients with TBI, we administered the *Wisconsin Card Sorting Test* (WCST) (82,83). In particular, although the WCST provides six different scores, due to its internal structure many studies normally rely on a maximum of two or three scores as an index of patients' performance (84–90). Therefore, in the present study, we utilized the *number of categories completed* and the *percentage of perseverative responses* as measures of *cognitive flexibility* (81).

Neuropsychiatric and psychological assessment

To assess apathy in this study, the Neuropsychiatric Inventory (NPI) (2,91,92) was administered to a relative of the enrolled patients. The NPI provides a comprehensive assessment of psychopathology in patients with neurological problems; it consists of an informant-based interview, which evaluates behavioral changes secondary to a neurological illness. Each NPI subscale assesses a different area: delusions, hallucinations, agitation/aggression, dysphoria/depressed mood, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor behavior, night-time disturbances and appetite/eating disturbances. The score for each neuropsychiatric domain is the product of the frequency and severity subscore for that particular domain (maximum 12), with 0 indicating the absence of symptoms and 12 indicating higher frequency and severity of symptoms.

To assess anxiety and depression, the State-Trait Anxiety Inventory (STAI X1-X2) (93) and the Hamilton Depression Rating Scale (HDRS) (94) were, respectively, administered. The STAI is a self-report scale that measures two separate concepts related to anxiety: the state of anxiety (STAI_X1) and anxiety as a trait (STAI_X2). STAI_X1 consists of 20 descriptive statements regarding how the participant is feeling at the moment of the interview; STAI_X2, instead, consists of 20 descriptive statements regarding how the participant usually feels. For both sub-scales, the total score can range from 20 (very low anxiety) to 80 (very high anxiety). The HDRS is a structured interview used to provide an indication of depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss and somatic symptoms and as a guide to evaluate

Table 1. Comparison of persons with a history of severe traumatic brain injury (sTBI) with age matched normal controls on measures used to sample self-awareness of functional daily activities (i.e. PCRS), anxiety (STAI-X1 and X2), depression (HDRS), alexithymia (TAS-20), neuropsychiatric disturbances (NPI) and performance on a cognitive measure of abstract reasoning and planning (WCST). Various measures of the severity of TBI and level of disability are also listed for the sTBI group.

	TBIs		HCs			
Sex (M; F)	22	8	22	8		
Handedness (Right; Left)	29	1	28	2		
	Mean	**St. Dev**	**Mean**	**St. Dev**	**Test**	**Sig.**
Age (years)	31.07	13.53	31.53	13.54	.018	NS
Educational level	13.07	3.23	14.27	2.98	2.238	NS
Disturbance of consciousness (days)	21.50	17.31				
Chronicity (days)	358.37	253.32				
GOS (median value = 4)	3.90	.55				
DRS (median value = 4)	4.07	2.05				
LCF (median value = 8)	7.50	.51				
DRS (median value = 4)	4.07	2.05				
LCF (median value = 8)	7.50	.51				
PCRS DS	3.17	14.44	−6.67	11.50	8.510	.005
TAS-20 *total score*	46.33	12.31	42.80	10.69	1.41	NS
STAI-X1	38.20	11.91	36.27	10.97	.43	NS
STAI-X2	38.90	13.15	36.27	10.97	.53	NS
HDRS	9.63	5.71	6.40	6.33	4.136	.047
NPI positive symptoms	11.07	10.37	1.80	3.35	21.7	<.001
NPI negative symptoms	1.93	3.33	.40	1.22	5.6	.021
WCST nr. Categories completed	4.33	2.26	5.67	1.09	8.436	.005
WCST % of perseverative responses	21.58	23.89	10.60	6.95	5.842	.019

Legend
GOS: Glasgow Outcome Scale
DRS: Disability Rating Scale
LCF: Level of Cognitive Functioning
PCRS: Patient Competency Rating Scale
TAS-20: Toronto Alexithymia Scale
STAI-*X1*: State-Trait Anxiety Inventory – *state anxiety*
STAI-*X2*: State-Trait Anxiety Inventory – *trait anxiety*
HDRS: Hamilton Depression Rating Scale
NPI: Neuropsychiatric Inventory
HDRS: Hamilton Depression Rating Scale
WCST: Wisconsin Card Sorting Test

recovery. Each item on the questionnaire is scored on a 3- or 5-point scale, depending on the item. In neurological populations, a cut-off point of 18 has been established to indicate the presence of clinically relevant depression (95).

Finally, we assessed alexithymia by administering all patients the Toronto Alexithymia Scale (TAS-20) (13,14); this is a 20-item self-report questionnaire that includes three sub-scales: a) difficulty in *identifying feelings*, which is an *affective* construct that measures participants' ability to recognize their feelings; b) difficulty in *describing feelings*, which is an *affective* construct that measures patients' ability to (verbally) express their feelings; and c) *externally oriented thinking*, which is a *cognitive* construct that measures participants' tendency to focus on superficial events and to avoid thinking about emotions (13,14). The TAS-20 total score can range from 20 to 100 (a score of 61 indicates high alexithymia), and subscale scores (DIF: 7–35; DDF: 5–25; EOT: 8–40). It is the most widely used measure to assess alexithymia in persons with and without TBI and has been shown to have good internal consistency and test–retest reliability (13,14,96).

Self-awareness assessment: the Patient Competency Rating Scale (PCRS)

Given its psychometric properties and feasibility, we chose the Patient Competency Rating Scale (PCRS) out of the measurement methods and instruments reported in the literature to assess ISA in these populations of patients (97).

The PCRS was translated and validated in Italian in the past by some researchers in our group (5). Also in other cultures, such as the American (98,99), Hebrew (100), Japanese (101), Spanish (102) and English from New Zealand (27), the PCRS previously showed an overestimation of self-reported behavioral competencies in patients with severe TBI, evidencing no specific difficulties regarding its cultural adaptations.

The PCRS is a 30-item self-report questionnaire that requires patients and their relatives to make an independent judgment of perceived degree of competency demonstrated in several behavioral, cognitive and emotional situations using a 5-point Likert scale (ranging from 1, "Can't do", to 5, "Can do with ease"). Total PCRS scores range from 30 to 150, with higher scores indicating higher levels of perceived competency. Comparing the $PCRS_{PATIENT}$ ratings with those of a family member (that is, $PCRS_{PATIENT} - PCRS_{RELATIVE}$ scores = $PCRS_{DISCREPANCY\ SCORE}$) shows how realistic patients are in evaluating their limitations (103–107).

The reliability reported by Prigatano and Altman (28) for PCRS total scores was r = 0.97 for patients and r = 0.92 for relatives; significant ($p < .05$) test–retest correlations were reported for 27 (patient sample) and 28 (informants) of the 30 items (108). Fleming et al. (109) reported acceptable one-week test–retest reliability for patients with TBI using intra-class correlations (ICC r = .85). In the same study, internal consistency was strong for both patient ratings (Cronbach's alpha = .91, n = 55) and relatives ratings of patients (Cronbach's alpha = .93, n = 50).

The first study in which the PCRS was used to study ISA after TBI simply classified patients into three groups: 1) patient's self-report of functional competency on this scale was greater than

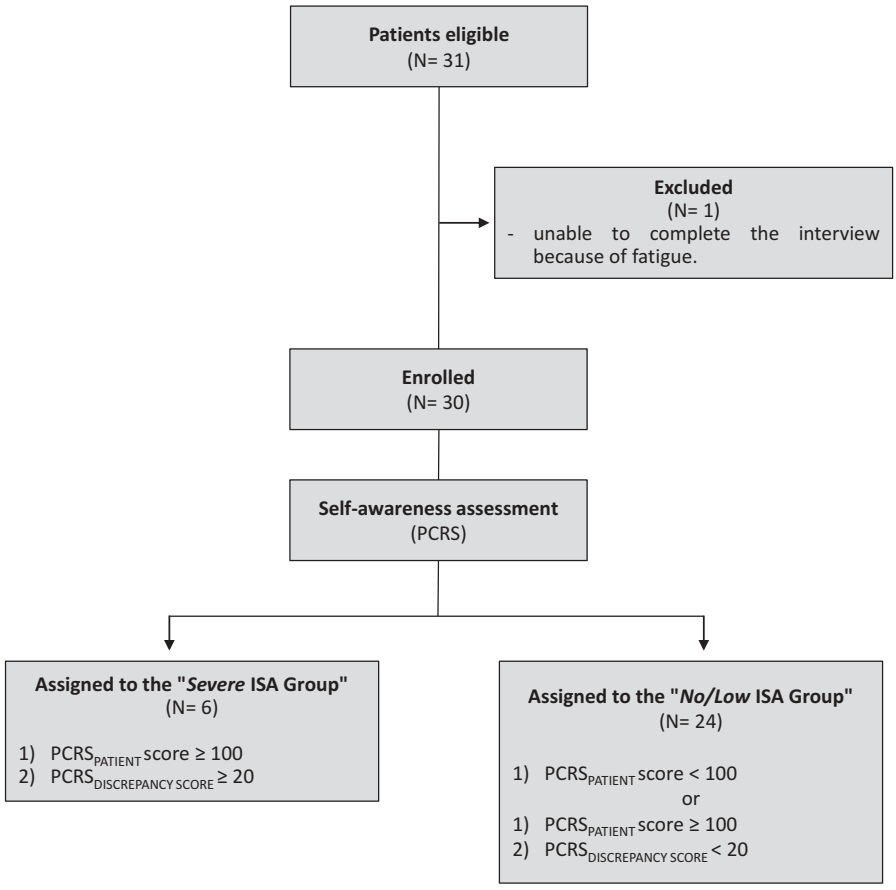

Figure 1. Patients sampling flowchart.

a relative's report (i.e., $PCRS_{PATIENT} > PCRS_{RELATIVE}$); 2) patient's self-report of functional competency on this scale was equal to relative's report (i.e. $PCRS_{PATIENT} = PCRS_{RELATIVE}$) and 3) patients who reported less functional competency on this scale compared to a relative's report (i.e., $PCRS_{PATIENT} < PCRS_{RELATIVE}$) (28). Over time, however, it became progressively clear that measuring ISA was a more difficult task. The magnitude of the difference between patients' self-reports and relatives' reports of patients' functional competency had to be taken into consideration. In a replication study, Prigatano (99) noted that "a PCRS score of 120+ indicates that the patient or relative believes that the individual can perform the activities (measured by this scale) 'fairly easily.' By contrast, a score of 90 "[…] indicates 'some difficulty in carrying out activities' measured by this scale" (pg. 193). He reported that patients' mean score on the PCRS was 125.1 compared to control group's ratings of 105.3. Thus, a 20 points positive $PCRS_{DISCREPANCY\ SCORE}$ may be helpful in identifying patients with TBI and ISA. In evaluating patterns of ISA observed in clinical practice, Prigatano (36) more recently reported that a patient with severe TBI who demonstrated persistent and severe ISA over a 25-year period of time self-reported high PCRS scores (ranging from 128 to 143); by contrast, his mother's PCRS ratings of him were at least 22 points lower than those he reported.

Based on these observations, we suggest using a double criterion to identify patients with severe ISA after severe TBI: a) the *$PCRS_{PATIENT}$ total score should be at least 100 points*, suggesting that patients perceive themselves as having minimal difficulties carrying out the various daily functions sampled by the PCRS; and b) a positive $PCRS_{DISCREPANCY\ SCORE}$ of *at least 20 points* (see flow chart (Figure 1)).

Procedure

The participants met the examiners three times. The first time their relatives were also present. At this time, the experimental procedure was explained and participants' informed consent was obtained. The neuropsychological assessment and administration of self-report scales took place on three different days to avoid tiring the patients. A neurologist made a functional assessment of the patients using the GOS and DRS scales; a neuropsychologist administered the WCST; a clinical psychologist administered the PCRS, STAI, TAS-20 and HDRS to the patients at the first session and in a later session administered the PCRS (*Relative* form) and the NPI to their relatives. To avoid any bias due to the different administration order, all of the assessment materials were administered in the same order.

Statistical analysis

To investigate differences between TBI and HCs regarding socio-demographic and cognitive-behavioral variables, series of individual one-way ANOVAS were performed. *Independent* variables were the two Groups of participants (TBI vs. HCs); *dependent* variables were age, educational level, PCRS, STAI-X1 and -X2, HDRS, TAS-20 and NPI, and two WCST sub-scores (Table 1).

To study the potential association between ISA and cognitive and affective disturbances, we first split the TBI sample into two subgroups based on their PCRS-DS scores. In particular, individuals with $PCRS_{DISCREPANCY\ SCORES} \geq 20$, *when* the $PCRS_{PATIENT}$ score was ≥100, were classified as having severe ISA; all other cases were classified as having low/no ISA (see Table 2 for details). Second, we performed series of Student T-tests for independent samples with Group (patients with severe ISA vs. patients with no/low ISA) as *independent* variable and measures above as *dependent* variables (Table 3).

To investigate the relationship in the TBI sample among ISA, cognitive flexibility and level of anxiety, depression and apathy, Pearson's r correlation analyses were also carried out between $PCRS_{DISCREPANCY\ SCORES}$ and subjects' scores on the WCST, the HDRS, STAI-X2 and on the apathy sub-scale of the NPI (Table 4).

Results

Clinical characteristics of individuals with TBI and comparisons between TBI and HC groups

Table 1 lists various measures of TBI severity as well as level of disability (i.e., duration of DoC, chronicity, GOS, DRS and LCF scores) for the sTBI group. The Table also shows the absence of differences between HCs and patients with severe TBI for age, sex and educational level. The two groups were significantly different in terms of *self-awareness* (i.e., we found higher $PCRS_{DISCREPANCY\ SCORES}$ in TBIs, indicating, in general, lower levels of self-awareness in patients than in HCs; $p = .05$), *depression* (higher HDRS scores in TBIs, i.e., patients were more depressed; $p < .05$), *positive* ($p < .01$) and *negative* ($p < .05$) *neuropsychiatric* symptoms (higher NPI scores in TBs,

Table 2. Distribution of PCRS scores of sTBI patients and their relatives in comparison to age matched HC subjects and their relatives.

	TBIs			HCs		
	Patients scores	Rel scores	P-Rel DS scores	HC scores	HC's Rel scores	HC-HC's Rel DS scores
Severe ISA	138	108	30	139	122	17
	135	108	27	148	141	7
	101	78	23	150	143	7
	118	97	21	146	141	5
	119	98	21	143	138	5
	125	104	21	145	141	4
	146	127	19	145	143	2
	115	97	18	136	134	2
	144	131	13	132	131	1
	148	135	13	150	150	0
	150	144	6	133	135	−2
	115	97	18	136	134	2
No/Low ISA	138	135	3	130	132	−2
	102	100	2	131	134	−3
	147	145	2	136	141	−5
	133	133	0	134	140	−6
	137	138	−1	132	139	−7
	90	92	−2	137	144	−7
	102	104	−2	105	115	−10
	104	108	−4	140	150	−10
	141	145	−4	133	145	−12
	105	111	−6	114	126	−12
	125	131	−6	131	143	−12
	96	103	−7	126	139	−13
	102	112	−10	131	148	−17
	132	143	−11	115	132	−17
	96	102	−12	128	146	−18
	121	134	−13	124	147	−23
	104	120	−16	114	146	−32
	101	130	−29	95	130	−35

Table 3. Comparison between TBI patients with severe ISA and with no/low ISA on the variables listed in Table 1.

		No/Low ISA N = 24		Severe ISA N = 6		P (T-test 1-tale)
Sex (M;F)		18	6	4	2	
Handedness (Right; Left)		23	1	6	0	
Age	Mean	29.63		36.83		.17
	St. dev.	12.84		15.94		
Ed. Lev.	Mean	13.42		11.67		.17
	St. dev.	3.05		3.83		
Disturbance of Consciousness (day)	Mean	18.83		32.17		.09
	St. dev.	12.49		29.16		
Chronicity (days)	Mean	327.96		480		.19
	St. dev.	246.7		264.65		
GOS	Mean	4		3.5		.04
	St. dev.	0.51		0.55		
DRS	Mean	3.79		5.17		.14
	St. dev.	1.56		3.37		
LCF	Mean	7.63		7		.005
	St. dev.	0.49		0		
TAS-20 total score	Mean	45.6		49.3		.3
	St. dev.	11.7		15.2		
TAS 1 sub-score	Mean	15.8		16.5		.44
	St. dev.	6.7		9.9		
TAS 2 sub-score	Mean	10.8		11.3		.41
	St. dev.	3.9		4.6		
TAS 3 sub-score	Mean	18.9		21.5		.051
	St. dev.	4.4		2.7		
STAI-X1	Mean	40.1		30.8		.008
	St. dev.	12.4		5.9		
STAI-X2	Mean	38.5		40.3		.411
	St. dev.	12.2		17.8		
HDRS	Mean	10.6		5.7		.023
	St. dev.	5.7		4.5		
NPI total score	Mean	11.4		19.3		.034
	St. dev.	12.2		7.5		
NPI positive score	Mean	10.1		15		.103
	St. dev.	10.9		7.1		
NPI negative score	Mean	1.3		4.3		.071
	St. dev.	2.9		4.1		
NPI depression sub-scale	Mean	0.54		1		.37
	St. dev.	1.06		1.26		
NPI apathy sub-scale	Mean	0.79		3.33		.067
	St. dev.	2.3		4.84		
WCST nr. categories completed	Mean	4.8		2.5		.039
	St. dev.	1.9		2.5		
WCST % of perseverative responses	Mean	15.8		44.7		.027
	St. dev.	19.3		28.1		

indicating a greater incidence of neuropsychiatric symptoms in patients than in HCs), and cognitive inflexibility (as documented by significant effects on the WCST indexes considered; $p < .05$ on all measures used when scoring the WCST). No other group differences were found (i.e., TAS-20 total score, and STAI-*X1* and – *X2* scores).

Comparisons between patients with TBI and HCs on PCRS

Table 2 shows the distribution of PCRS scores of patients with severe TBI and their relatives compared to the PCRS scores of HCs and their informants (i.e., relatives or significant others who knew them well). Severe ISA was defined using the above criterion of a positive $PCRS_{DISCREPANCY\ SCORE}$ of at least 20 points when the $PCRS_{PATIENT}$ score was at least 100. We found that 20% of the patients with TBI (6 out of 30) showed *severe* ISA. By contrast, this was not shown by any of the HCs. Table 2 also reveals that it was more likely that HCs would underestimate their abilities compared to patients with TBI who, as a group, overestimated their abilities relative to reports (see also Table 1).

Comparisons of patients with severe ISA and with no/low ISA

As illustrated in Table 3, patients with severe ISA presented an average length of DoC of over 32 days, whereas those who showed no/minimal ISA had an average length of DoC of 18.8 days. ($p = .09$). As for the functional measures, patients with *severe* ISA showed lower GOS ($p < .05$) and LCF ($p < .01$) mean scores (both indicating a worse outcome) than those with *no/low* ISA. Patients with *no/low* ISA showed higher levels of depression (i.e., HDRS score) and *state* anxiety (STAI-*X1* score) ($p < .05$ in both cases) and a lower expression of neuropsychiatric symptoms (i.e., NPI total score; $p < .05$) than those with *severe* ISA. In particular, this latter group tended to be relatively more apathetic ($p = .067$) and alexithymic ($TAS\text{-}20_{factor\ 3}$ score; $p = .051$) than patients with *no/low* ISA and performed worse on the WCST ($p < .05$ in both cases). Moreover, patients with severe TBI and severe ISA appeared to have more severe brain injuries with more severe cognitive impairments in terms of cognitive flexibility.

Table 4. Correlational Matrix on selected affect and cognitive variables in the TBI group (Sig. 2-tailed; N = 30).

	PCRS Discr.sc.	NPI Apathy	HDRS	STAI-*X2*	WCST *nr. of categories achieved*	WCST *% of pers. errors*
PCRS Discrepancy scores						
NPI Apathy	.305 .101					
HDRS	−.345 *.062*	.308 .097				
STAI-*X2*	−.232 .218	.218 .247	**.571**** **.001**			
WCST *nr. of categories achieved*	−.115 .547	−.384* .036	−.299 .109	−.339 *.067*		
WCST *% of perseverative errors*	.258 .168	.434* .017	.128 .501	.276 .139	**−.797**** **.000**	

Legend
NPI: Neuropsychiatric Inventory
HDRS: Hamilton Depression Rating Scale
STAI-X1: State-Trate Anxiety Inventory – state anxiety
STAI-X2: State-Trate Anxiety Inventory – trate anxiety
WCST: Wisconsin Card Sorting Test
** p < 0.01
*p < 0.05

Correlations between performance on WCST and self-awareness, anxiety, depression and apathy scores in the TBI group

Table 4 summarizes the correlational findings based on the entire severe TBI sample. As expected, apathy (i.e., NPI apathy sub-score) correlated with both measures of cognitive flexibility [i.e., negatively with the WCST *nr. of categories achieved* and positively with WCST % of *perseverative responses* ($p < .05$ in both cases)]; that is, more apathetic patients with TBI performed consistently worse on the WCST. Also, as predicted, the level of depression in this TBI sample was not related to performance on the WCST but, as expected, it tended to be negatively correlated with the level of ISA (r = +-.345; $p = .062$); that is, the higher the $PCRS_{DISCREPANCY\ SCORES}$ (i.e., the level of patients' ISA), the lower their level of depression. Depression and trait anxiety were also significantly correlated (r = +0.571; $p < .001$) in this TBI sample.

Discussion

The first aim of the present study was to determine the frequency of severe ISA in a sample of patients with a history of severe TBI compared to a demographically matched normal control group, and its association with selected *clinical, neuropsychiatric* and *cognitive* variables. The second goal of the study was to compare patients who had severe ISA with those who had no or minimal ISA mainly in terms of depression and apathy.

General results of our patients with TBI show that they performed worse than HCs on neuropsychological tests requiring cognitive flexibility, overestimated their functional abilities (as reflected by the $PCRS_{DISCREPANCY\ SCORES}$) and showed more severe neuropsychiatric problems (as judged by their relatives via the NPI for both positive and negative symptoms). These results are in line with previous investigations of different TBI populations (3,5–10,27–30,81,89,106,110–112).

As for the main goal of the present study, our findings provide preliminary evidence regarding the advisability of adopting specific cut-off scores when using the PCRS to help judge the severity of ISA. If a 10-point cut-off score disparity is used to capture "*moderate*" ISA, then 30% of this sample of patients with severe TBI showed *moderate to severe* ISA. This finding is compatible with what has been previously reported in the literature (113), adding reliability to our results. Moreover, using the suggested cut-off score for severe ISA of *at least 20 points* of disparity on the PCRS *when the* $PCRS_{PATIENT}$ *score was at least 100*, then 20% of the sample showed this pattern. No HCs showed a $PCRS_{DISCREPANCY\ SCORE} \geq 20$, thus evidencing the good specificity of the PCRS using this cut-off point. However, this method of judging the severity of ISA needs to be replicated in larger samples to confirm its reliability.

Patients with severe ISA also obtained worse GOS and LCF scale scores than those with no/low ISA. These results are in line with those of studies which underlined that a higher level of ISA can be associated with worse functional outcome (29,31–35).

Moreover, while it is well established that patients with severe TBI are more likely to show ISA (28–30), the present findings suggest that the duration of the DoC could have an important role in determining the severity of ISA several months post brain injury. All of the patients studied had a history of severe TBI and DoC, but those with severe ISA presented on average a DoC of over 32 days, whereas those with severe TBI who did not show severe ISA or showed minimal ISA had a DoC for an average of 18.8 days. Although not statistically significant ($p = .09$), these differences are compatible with the theoretical proposition that disturbances in self-awareness after TBI may actually be a residual form of disturbances of consciousness even though the patient has emerged from coma (37). Additional studies on larger cohorts of patients are needed to confirm this hypothesis.

Another interesting result emerged from the investigation of the relationship between some executive dysfunctions and ISA. On both indexes used to assess cognitive inflexibility via the WCST, patients with severe TBI performed worse than those with no or minimal ISA. Our results are in line with those of many studies that found a close relationship between worse performance on cognitive flexibility tasks and lower levels of self-awareness after severe TBI (5,55–57,114,115; but see also 60,61 for divergent results). Interestingly, our findings are compatible with the observations of Ham et al. (116) which suggest that failure to monitor one's errors while performing a vigilance task is associated with behavioral markers of ISA in patients with TBI. The above data seem to support the hypothesis that both executive system and self-awareness (at its metacognitive level) may co-determine higher order control over "lower" aspects of cognition (52,53).

While it is important to note that patients with severe ISA are often more seriously injured than patients with severe TBI

with no or minimal ISA, the present findings bring attention to the fact that important emotional features of ISA are relevant for understanding these phenomena. In the group of patients with severe TBI, those with severe ISA had more severe cognitive impairments but were less depressed and anxious than patients with no or mild ISA, as predicted. Also, the correlational analysis showed a trend toward statistical significance between self-awareness and depression. These findings confirm those of a series of studies that found a clear relationship between self-awareness and the presence of mood disorders or ****emotional distress (32,54,57,66,67,117-130). Patients with severe ISA also showed the opposite tendency to appear more apathetic and to have greater difficulty describing their feelings. This finding is reminiscent of the early observations of Babinski on anosodiaphoria (39). The patients do not voice anxiety or depression even when they begin to discover their severe motor impairments; rather, they seem unconcerned and have difficulty descripting their emotional state. Further exploration of these emotional features is warranted to better understand the phenomena of ISA. Prigatano (131) argued that disturbances of ISA reflect a disruption of the integration of feelings and thinking. The present findings support this broad hypothesis. It can also be hypothesized that anosodiaphoria also reflects this disruption. Indeed, patients with severe ISA might not show that they have adequate emotions (expected to be related to the consequences of the injury) because of a disconnection between cortical brain regions (responsible for thoughts) and deep brain regions (responsible for feelings). In this regard, a specific tool is needed to directly investigate anosodiaphoria. In fact, it is very important to differentiate anosodiaphoria as an "aspect of apathy" from all other symptoms of apathy (such as a decrease in activities, inattention to usual interests, loss of interest in plans of family members or other relevant people, reluctance to start a conversation, being less spontaneous or loving, etc.).

The small size of the sample of patients with severe TBI and the unbalanced number of unaware patients compared to those with no/low ISA could represent one limit of the present study, and the choice to not apply correction for multiple comparisons could increase the risk of alpha inflation. However, this choice was made in order to avoid the risk of a type II error (accepting a false null hypothesis), which is relatively high with such a small sample. In view of this consideration, caution should be taken in generalizing the results of the present study to other TBI samples. In fact, the study should be replicated in larger cohorts of patients with severe TBI that are better balanced for level of ISA.

Finally, it is worth noting that in the present study cognitive flexibility was measured using a single instrument, i.e., the WCST. Although this is a well-known, useful measure of executive functioning, it is known to have relatively weak reliability (85,132). Additional studies should be carried out to assess a wider range of executive functions with a more extensive evaluation battery.

Nevertheless, despite these limitations, it should be considered that our results derive from both correlational analyses of cognitive, emotional variables and caregiver reports, which strengthen the credibility of the results.

Conclusions

Although the results of this study are preliminary and need confirmation in future investigations, they have some important clinical implications.

First, they support the clinical impression that the diagnosis and treatment of severe ISA is important for functional outcome (29,31–35). Second, this study suggests that there are two opposite emotional patterns related to different levels of ISA: high levels of ISA seem mainly related to *neurological* disturbances (such as apathy and/or anosodiaphoria); good or minimal impairment of self-awareness were found to be mainly related to the presence of *psychological* reactions (i.e., depression, in particular, but also anxiety). These results suggest the need to orient rehabilitation programs toward different courses depending on levels of ISA. In fact, on one hand, in cases of poor self-awareness (and probable parallel worse cognitive features) clinicians should approach patients primarily with a *neuropsychological* perspective, treating their cognitive difficulties as well as helping them to increase their knowledge of brain damage and its consequences (i.e., treating ISA). At the same time, patients should be treated for their diminished concern about the illness or disability (i.e., apathy). On the other hand, when patients show no (or improved levels of) ISA, clinicians should treat them mainly using a *psychological* perspective in order to treat mood disorders closely associated with their self-awareness.

In summary, this study underlines the need to consider and treat the individuals who have sustained severe traumatic brain damage from different perspectives, i.e., neuropsychological, neuropsychiatric and neuropsychotherapeutic, in a holistic and *inter*-professional perspective, which is one of the main challenges in the area of rehabilitation.

Acknowledgments

The authors would also like to thank Chiara Falletta Caravasso for her support during the data collection, and Teresa Donvito and Ludovica Mastrilli for their assistance in editing the final version of the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

Funding

This research was supported by grants from the "Barrow Foundation UK", which allowed time for George P. Prigatano to prepare portions of this paper.

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