NEUROBEHAVIORAL CHANGES AFTER ACQUIRED BRAIN INJURY

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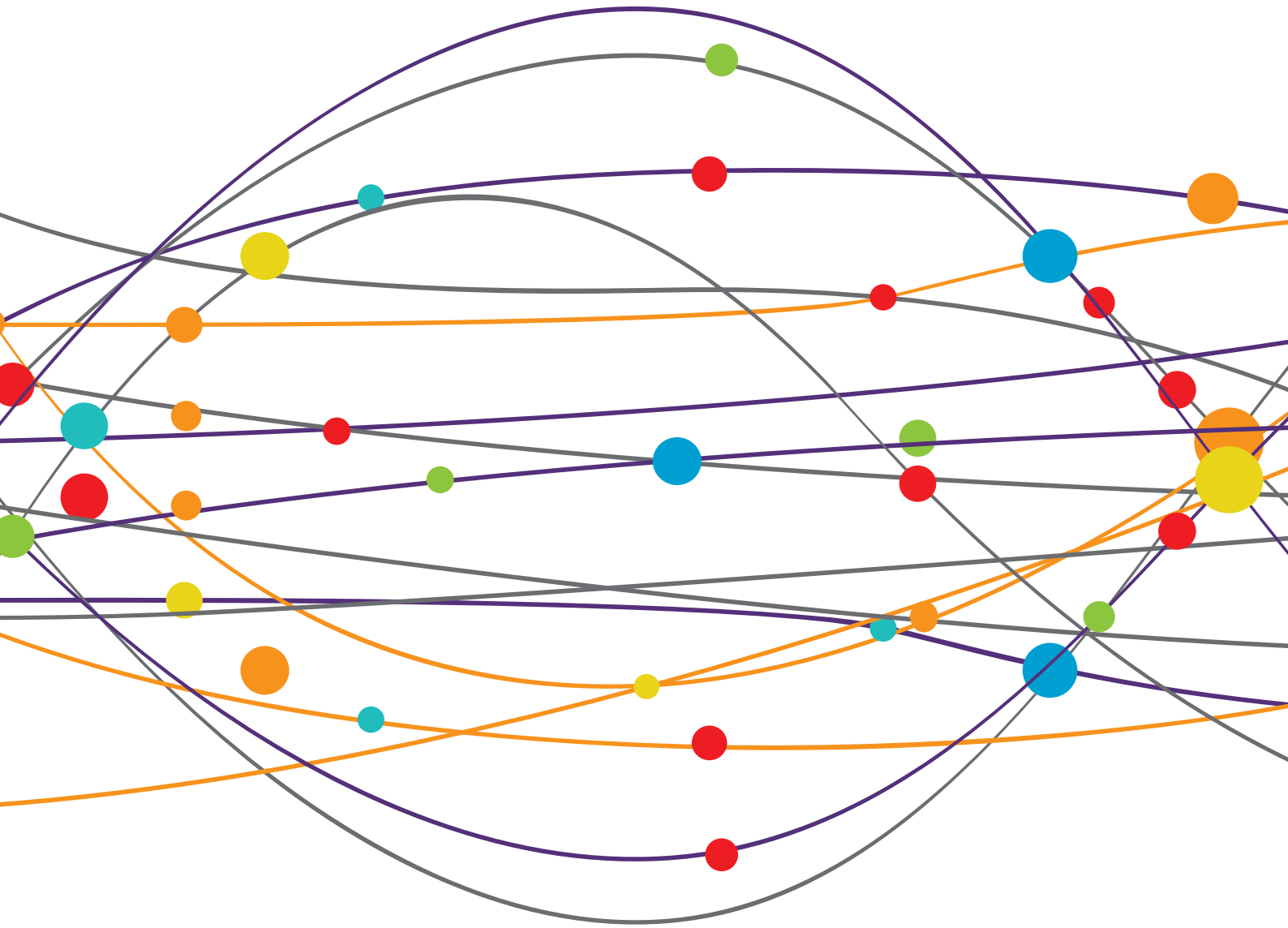

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NEUROBEHAVIORAL CHANGES AFTER ACQUIRED BRAIN INJURY

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Table of Contents

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Default Mode Network Connectivity Predicts Emotion Recognition and Social Integration After Traumatic Brain Injury

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Moderate-severe traumatic brain injury (TBI) may result in difficulty with emotion recognition, which has negative implications for social functioning. As aspects of social cognition have been linked to resting-state functional connectivity (RSFC) in the default mode network (DMN), we sought to determine whether DMN connectivity strength predicts emotion recognition and level of social integration in TBI. To this end, we examined emotion recognition ability of 21 individuals with TBI and 27 healthy controls in relation to RSFC between DMN regions. Across all participants, decreased emotion recognition ability was related to increased connectivity between dorsomedial prefrontal cortex (dmPFC) and temporal regions (temporal pole and parahippocampal gyrus). Furthermore, within the TBI group, connectivity between dmPFC and parahippocampal gyrus predicted level of social integration on the Community Integration Questionnaire, an important index of post-injury social functioning in TBI. This finding was not explained by emotion recognition ability, indicating that DMN connectivity predicts social functioning independent of emotion recognition. These results advance our understanding of the neural underpinnings of emotional and social processes in both healthy and injured brains, and suggest that RSFC may be an important marker of social outcomes in individuals with TBI.

Keywords: traumatic brain injury, emotion recognition, resting state functional connectivity, default mode network, community integration, TBI, DMN

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INTRODUCTION

Our ability to perceive and understand the emotions of others is crucial to successfully navigating social interactions and living in a social milieu. Because emotion recognition is a core social cognitive process, those with deficits in this ability—for instance, due to psychiatric condition or disease status—tend to have poorer outcomes in many domains of social functioning, such as successfully communicating with others (1), maintaining occupation (2), and participating in the community (3). Similarly, there exists a spectrum of emotion recognition ability within the healthy neurotypical population whereby greater recognition ability is associated with social competence and maintaining peer relationships (4, 5).

Deficits in emotion recognition are a pervasive yet under acknowledged aspect of traumatic brain injury (TBI). It is estimated that up to 39% of individuals with moderate-severe TBI suffer

from significant emotion recognition deficits, with the degree of impairment approximating a standard deviation difference from the performance of healthy individuals (6). In TBI, these emotion recognition impairments predict a number of social, cognitive, and behavioral issues such as deficits in self-awareness, behavioral inhibition and emotion regulation (7, 8), social communication (9), and social competence (7).

As the nature of injury in individuals with TBI is diffuse and heterogeneous (10), the specific neurobiological substrates of social cognitive deficits in TBI are still being identified. While some have examined these deficits using task-based fMRI experiments (11), and structural studies (12–14), there is growing interest in using the brain's intrinsic functional connectivity to explain deficits in TBI (15, 16). For instance, resting state functional connectivity (RSFC) can be used to predict cognitive and behavioral outcomes for individuals with TBI who do not have detectable anomalies in brain structure (17).

Of particular interest is the default mode network (DMN), a functional network that captured scientific interest when it was found to be robustly activated during periods of rest (18, 19). Aberrant functional connectivity within the DMN has been demonstrated in TBI, predicting impairments in cognition (20–22), and functional outcomes like depression and fatigue (22). Furthermore, the DMN is particularly relevant to social cognition as the regions comprising the DMN are also engaged during social and emotional processes (23, 24). It has been argued that DMN RSFC may represent a neuromarker of individual differences in social abilities, predicting mentalizing ability in neurotypicals (25), predicting autistic traits in neurotypicals and people with autism (26), and predicting social network size in macaques (23) and humans (27). While DMN RSFC is an important and flexible tool for investigating social cognition and behavior, it is currently unclear how it relates specifically to the component process of emotion recognition ability. Although the regions comprising the DMN have been linked to emotion recognition in task-based paradigms (28), there is little work examining individual differences in emotion recognition using DMN RSFC. It is unknown how RSFC patterns within the DMN are related to emotion recognition ability in healthy neurotypicals, how these relationships may differ in TBI, and whether they are predictive of socially-relevant functional outcomes.

To address these gaps in the literature, the current work investigated RSFC within the DMN (hereafter referred to as "DMN connectivity") in relation to emotion recognition in healthy individuals and those with moderate-severe TBI. We hypothesized that DMN connectivity would be associated with individual differences in emotion recognition ability, and further examined whether these relationships were altered in the context of TBI. We also sought to test the hypothesis that emotion recognition deficits contribute to social functioning problems after TBI by examining the extent to which emotion recognition ability predict a real-world measure of post-injury community integration. Furthermore, as prior work has suggested that RSFC may be independently related to social functioning (29, 30), we will test whether DMN connectivity is a stronger predictor of community integration than emotion recognition ability—this finding would suggest that DMN connectivity could be used within rehabilitation research as a predictive tool or as a treatment target.

METHODS

Participants

A total of 53 people participated in the current research (25 TBI and 28 healthy controls [HC]). Participants with TBI were identified through our participant database, which comprises individuals recruited originally from local hospitals and the general community. Eligible participants sustained a single, closed-head moderate or severe TBI. The severity of the TBI was determined using the Mayo Classification System criteria (31), which for the current study were any of the following: (1) loss of consciousness for 30 min or more, (2) post-traumatic anterograde amnesia for 24 h or more, (3) lowest Glasgow Coma Score in the first 24 h $\leq$ 12, or (4) evidence of significant neurological injury on CT/MRI (e.g., subdural hematoma, cerebral contusion, subarachnoid hemorrhage). Injury severity was confirmed from medical records when possible; in the absence of medical records, severity was determined family member attestations of the length of loss of consciousness/coma. Participants were deemed eligible for the study if they were at least 12 months post injury. Injury characteristics for participants with TBI are presented in **Table 1**. HC participants were recruited from the general community and had no history of head trauma or neurological disorder. Four participants (1 HC and 3 TBI) were excluded due to excessive head motion, and one TBI participant was excluded due to an outlying low score on the emotion recognition task (more than three standard deviations from the mean), leaving a final sample of 21 TBI and 27 HC. Participant groups did not significantly differ on mean age or education, or sex distribution as seen in **Table 2**. Participants completed behavioral measures (neuropsychological testing, social cognitive tasks, and self-report questionnaires) in an initial testing session and were scanned ∼1 week later at an adjacent imaging facility [M = 8.44 (10.61) days]. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Kessler Foundation Institutional Review Board.

Assessment of Emotion Recognition

We employed a measure that has previously been validated for use in the TBI population, The Awareness of Social Inference Test [TASIT; (32)], which includes multiple subtests that tap into different aspects of social cognitive ability. In the current study, we examined the TASIT Emotion Evaluation Task, which assesses emotion recognition ability via a sequence of short (15–60 s) videotaped vignettes featuring interactions among trained actors. Participants were instructed to view each vignette and identify which emotion was being conveyed by the actor from a choice of seven basic emotions (neutral, surprised, anxious, sad, angry, revolted, and happy). Four instances of each emotion were presented in vignettes in

TABLE 1 | Injury characteristics for TBI participants.

Nature of injury	GCS score	PTA	LOC	Neuroradiological findings
Fall	8			Epidural hematoma
MVA	13			Cerebral contusion
Unknown			>30 min	
Fall	5			Subarachnoid hemorrhage, cerebral contusion
MVA	6			Hemorrhagic contusion, subarachnoid hemorrhage
Fall	9			Subdural hematoma, intracerebral hemorrhage, subarachnoid hemorrhage
MVA			6 weeks	
MVA	4			
Assault			>30 min	
Fall	14	∼36 h		
MVA	13			Epidural hematoma; subdural hematoma, subarachnoid hemorrhage
MVA	3			
MVA				Diffuse axonal injury
motorcycle accident			>30 min	
MVA	11			Cerebral contusion
Fall				Epidural hematoma
Fall	15			Subarachnoid hemorrhage
Fall	15			Subarachnoid hemorrhage, multiple contusions
MVA			35 days	
Struck by vehicle				Intracerebral hemorrhage, subdural hemorrhage
MVA	3			Subdural hemorrhage, intracerebral hemorrhage

GCS, Glasgow Coma Scale; PTA, post-traumatic amnesia; LOC, loss of consciousness; MVA, motor vehicle accident.

TABLE 2 | Demographic and performance information for study participants.

	TBI	HC	*t*	*p*
	Mean (*SD*)	Mean (*SD*)		
Demographics				
Age	41.71 (15.22)	38.00 (13.66)	0.89	0.379
Education	14.64 (1.92)	15.48 (1.93)	−1.50	0.141
Months since injury	112.47 (97.95)	–	–	–
			x^2	*p*
Gender	3F/18M	9F/18M	2.29	0.185
Performance				
TASIT performance	22.52 (2.60)	24.78 (1.72)	−3.61	0.001
Cognitive composite score	0.30 (0.76)	−0.38 (0.78)	−3.00	0.004

a pseudorandomized sequence; this presentation order was consistent across all participants. A sum of correct responses for all trials was computed with a maximum attainable score of 28.

Neuropsychological Assessment

Participants completed a battery of neuropsychological tests sensitive to the primary neurocognitive deficits seen in TBI, including processing speed, attention, and executive functioning. These cognitive domains also have been shown to influence aspects of social cognition across various clinical disorders [e.g., (33–35)]. Therefore, we examined the potential influence of neuropsychological performance on emotion recognition analyses with a cognitive composite score, which was obtained by averaging z-scored performances on tests of processing speed, working memory, and executive functioning. Constituent tests included Block Design from the Wechsler Abbreviated Scale of Intelligence-II (36), Trail Making- Number-Letter Switching Condition and Color-Word Interference- Inhibition Condition from the Delis-Kaplan Executive Function System (37), and the Symbol Digit Modalities Test (38). This cognitive composite score was entered as a covariate in functional connectivity analyses.

Measurement of Community Integration

The Community Integration Questionnaire [CIQ; (39)] was designed for use with individuals with TBI to assess social integration, a fundamental component of recovery and rehabilitation that contributes importantly to positive post-injury outcome, including mental and physical health (40) and quality of life (41). This self-report questionnaire comprises three subscales, which index integration in home activities, productivity (employment or volunteer activities), and social activities. A widely used measure, the CIQ has demonstrated good validity and reliability within the TBI population (39, 42).

Image Acquisition

Imaging data were acquired using a Siemens Magneton 3T Skyra scanner (Siemens Corporation, Erlangen, Germany). Echo-planar imaging (EPI) was used to image the resting state, during which participants were instructed to lay still with eyes closed. EPI data were acquired over the course of 6 min, with 32 images of 3 mm thickness aligned AC-PC (180 volumes, TR = 2,000 ms, TE = 30 ms, flip angle = 70°, voxel size = 2.3 × 2.3 × 3 mm). Additionally, a high-resolution anatomical image was acquired for ∼5 min, with 176 slices of 1 mm thickness (TR = 2,100 ms, TE = 3.43 ms, flip angle = 9°, voxel size = 1 mm isotropic).

fMRI Pre-processing

Imaging data were pre-processed using Statistical Parametric Mapping software, SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Functional images were pre-processed using a standard pipeline, including slice-timing correction for interleaved slice acquisition, realignment of the image series to the first functional image, coregistration of functional, and structural images, tissue segmentation, and normalization of images to standard Montreal Neurological Institute (MNI) space using 12-parameter affine transformations and non-linear

registration. Images were smoothed using a 6 mm FWHM Gaussian kernel to improve the ratio of signal-to-noise. Motion correction was then applied (see below), and noise signals were estimated and removed using linear detrending, a bandpass filter of 0.01–0.12 Hz, and the aCompCor procedure (43) as implemented in the CONN toolbox (44). This method removes effects of white matter (WM) and cerebrospinal fluid (CSF) on the BOLD signal using the participant-specific WM and CSF masks, while avoiding the augmentation of negative correlations between voxels associated with global mean signal regression (45).

Default Mode Network (DMN) Connectivity

Functional connectivity analyses were performed with the CONN toolbox (44) using DMN regions of interest (ROIs) defined *a priori* from Power et al.'s cortical atlas (46). The DMN in this atlas comprises 58 ROIs in medial pre-frontal, posterior cingulate/precuneus, and bilateral temporal and temporoparietal regions. ROIs were defined as non-overlapping spheres of 10 mm diameter. In first-level analyses, BOLD timeseries were averaged across all voxels of each ROI and correlated with the remaining ROIs, such that for each participant, we obtained a DMN ROI-ROI correlation matrix. First-level correlations were then Fisher-transformed and subjected to second-level tests of ROI-to-ROI connectivity within the DMN, including (1) group differences (HC > TBI and TBI > HC) in connectivity and (2) correlation between emotion recognition ability and DMN connectivity across groups. All connectivity analyses employed FDR-correction ($\alpha = 0.05$) to control for multiple comparisons. Additionally, we extracted first-level connectivity values for connections showing significant relationships with emotion recognition at the group level. Using SPSS, we entered these values into regression analyses predicting community integration in individuals with TBI [analyses were constrained to individuals with TBI as a reduction in community integration is a common sequela of TBI; (47)].

Motion Artifacts

To correct for head movement, we used the ArtRepair toolbox (48), which addresses both multivolume and smaller motion perturbations. Following realignment, large amplitude motion correction was applied using trigonometric form adjustment. Rapid scan-to-scan motion was adjusted following normalization and smoothing. Volumes with more than 1 mm scan-to-scan movement (translation and rotation) were treated as artifacts and replaced with interpolated signal from adjacent, unaffected volumes. Participants with more than 20% artifactual volumes (four participants) were excluded from further analyses. In the remaining sample, TBI and HC groups did not differ on the number of artifactual volumes, $M_{TBI} = 5.86\ (9.33)$, $M_{HC} = 2.63\ (6.70)$, $t_{(46)} = 1.42$, $p = 0.16$.

RESULTS

Group Differences in Emotion Recognition Ability, Cognition, and Connectivity

Compared to HCs, the TBI group demonstrated significantly reduced emotion recognition ability as measured by the TASIT, $t_{(46)} = 3.61$, $p = 0.001$, and cognitive performance, $t_{(46)} = 3.00$, $p = 0.004$. However, there were no significant group differences in DMN connectivity metrics examined at the second level (*p-FDR* > 0.05).

Emotion Recognition Ability and DMN Connectivity

Across all participants, emotion recognition was inversely associated with connectivity between an ROI in dmPFC and three temporal lobe ROIs: two in left parahippocampal gyrus (parahipp) and one in right temporal pole (**Table 3**). Relationships between connection strength and emotion recognition scores are illustrated in **Figure 1**. There were no significant interactions between emotion recognition performance and group membership on DMN connectivity (all *p-FDR* values > 0.05).

Influence of Potential Confounding Variables on the Emotion Recognition-Connectivity Relationships

Emotion recognition ability was significantly correlated with general cognitive performance, $r_{(46)} = 0.44$, $p = 0.002$, age, $r_{(46)} = -0.51$, $p < 0.001$, months since injury, $r_{(19)} = -0.45$, $p = 0.039$, and was marginally associated with gender such that female participants had slightly higher recognition ability than males, $\beta = -0.27$, $t_{(46)} = -1.96$, $p = 0.061$. Level of education was not associated with emotion recognition ability, $r_{(46)} = 0.19$, $p = 0.188$. To ensure that demographic variables and group status did not unduly influence the relationship between emotion recognition and DMN connectivity metrics, we tested these covariates in linear regression analyses with each of the three connectivity metrics as dependent variables. We found that controlling for the influence of these covariates did not change the associations between emotion recognition and DMN

TABLE 3 | ROI-to-ROI connectivity associated with emotion recognition.

Connection	ROI 1	ROI 2	*t*	*p-FDR*
1	**dmPFC;** xyz = [−2, 38, 36]	**parahippocampal gyrus;** xyz = [−13, −40, 1]	−3.53	0.027
2		**parahippocampal gyrus/fusiform gyrus;** xyz = [−26, −40, −8]	−3.56	0.027
3		**temporal pole;** xyz = [46, 16,−30]	−3.34	0.032

ROI, region of interest, dmPFC, dorsomedial prefrontal cortex, xyz, coordinates of the centroid voxel of each ROI reported in Montreal Neurological Institute (MNI) stereotaxic space.

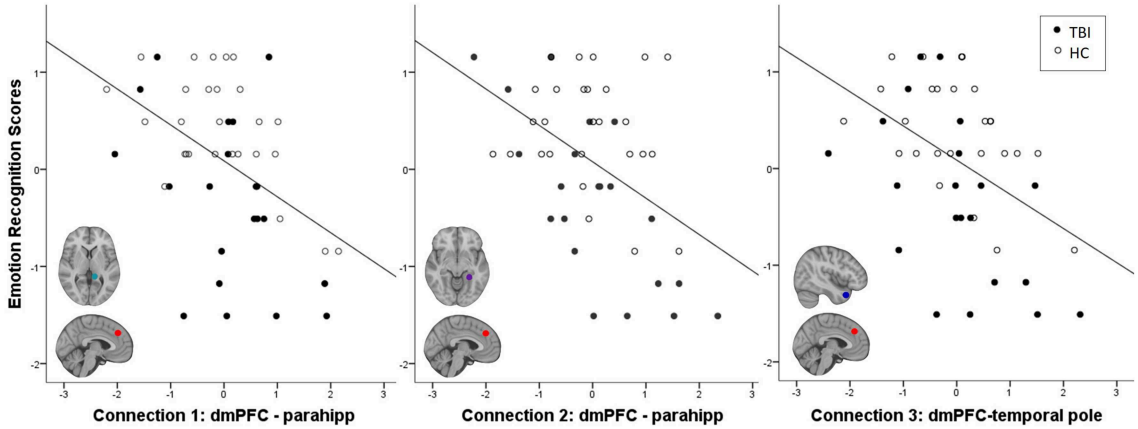

FIGURE 1 | Negative relationship between emotion recognition ability and frontal-temporal connectivity strength. Z-normalized TASIT scores are plotted again first level fisher-transformed correlation coefficients denoting the strength of functional connectivity between regions described in **Table 3**. Parahipp = parahippocampal gyrus.

connectivity. Results of these analyses are described further in **Supplementary Table 1**.

Connectivity Metrics and Community Integration

Finally, we were interested in whether the DMN connectivity metrics which we identified in the previous analysis could independently explain social functioning in TBI, over and above the influence of emotion recognition. To this end, we examined the relationships between the three DMN connections and TBI participants' level of community integration, controlling for emotion recognition. Indeed, within the TBI group, the first functional connectivity metric from **Table 3** (dmPFC-parahipp) was significantly inversely associated with total CIQ score, $r_{(18)} = -0.60$, $p = 0.005$ (the second and third connectivity metrics did not significantly correlate with CIQ, both $ps > 0.18$). Further, consistent with our previously reported finding (49), emotion recognition ability in the TBI sample was related to better community integration (total CIQ score), $r_{(18)} = 0.44$, $p = 0.051$. Thus, in order to test the incremental predictive value of the first DMN connectivity metric on community integration, controlling for participants' emotion recognition ability, we conducted a hierarchical multiple regression (see **Table 4**). Potential confounds such as gender ($\beta = -0.26$, $t_{(18)} = -1.12$, $p = 0.276$), education [$r_{(18)} = 0.135$, $p = 0.572$], cognitive ability [$r_{(18)} = 0.06$, $p = 0.798$], and months since injury [$r_{(18)} = -0.03$, $p = 0.914$] were not related to total CIQ score. However, age was a significant predictor of community integration [$r_{(18)} = -0.45$, $p = 0.045$] and is thus treated as a covariate in the analysis. In the first model, we entered emotion recognition ability (TASIT performance) as a predictor and participant age as a covariate; the model was marginally significant, $F_{(2,17)} = 3.09$, $p = 0.07$. In the second model, in addition to TASIT and age, we added the first DMN connectivity metric (dmPFC-parahipp) as a predictor and found that the overall model was significant, $F_{(3,16)} = 4.32$, $p = 0.021$, that DMN connectivity was a significant predictor of CIQ, $\beta = -0.47$, $t_{(16)} = -2.29$, $p = 0.036$, and explained an additional 18% of the variance. Furthermore, we examined the subscales of the CIQ and determined that this effect was being driven primarily by the Social Integration subscale, which was strongly associated with dmPFC-parahipp connectivity, $r_{(18)} = -0.58$, $p = 0.008$ (neither Home Integration nor Productivity were significantly related to functional connectivity, $ps > 0.65$). Together these data suggest that participants' frontal-temporal DMN connectivity at rest is predictive of the social aspects of community integration in TBI, and is a stronger predictor than their emotion recognition ability.

DISCUSSION

Impaired emotion recognition is prevalent in TBI and has deleterious social consequences, yet the neurobiological correlates of this impairment remain poorly understood. The current study examined DMN connectivity in relation to emotion recognition and social functioning in a sample of individuals with TBI and HCs. We found that while there were no significant group differences in DMN connectivity, there was a relationship between emotion recognition ability and frontal-temporal connectivity strength across groups. Moreover, frontal-temporal connectivity was predictive of social integration in the TBI group, even more robustly than their emotion recognition scores.

Across both groups, we found that greater frontal-temporal DMN connectivity (specifically dmPFC-parahipp and dmPFC-temporal pole) was associated with worse performance on an ecologically valid measure of emotion recognition, the Emotion Evaluation subtest of the TASIT (32). This result is consistent with a recent study in healthy individuals that found greater connectivity (specifically between the posterior DMN—inclusive of dmPFC—and regions including parahippocampal gyrus and temporal pole) was associated with worse performance on a test of emotion intelligence incorporating emotion recognition (50). The extension of these findings in the current study to include

TABLE 4 | Hierarchical linear regression testing associations between emotion recognition performance, DMN connectivity, and community integration.

		Model statistics		Model change				Predictors		
Models	**Predictors**	***F***	***p***	R^2	R^2 **change**	***F* change**	***p***	***β***	***t***	***p***
1	3.09	0.072	0.27	0.27	3.09	0.072				
Age							−0.31	−1.28	0.216	
TASIT performance							0.29	1.19	0.249	
2	4.32	0.021	0.45	0.18	5.25	0.036				
Age							−0.20	−0.89	0.387	
TASIT performance							0.18	0.82	0.426	
dmPFC-parahipp connectivity							−0.47	−2.29	0.036	

The dependent variable is total score on the CIQ.

individuals with neurologic compromise suggests that the injury-related pathophysiology contributing to emotion recognition deficits in TBI may lie at one end of the physiological continuum that also characterizes individual differences in healthy controls.

Altered DMN connectivity in relation to emotion recognition is also consistent with a larger literature describing dysregulation within and between DMN subsystems in a variety of mental health disorders involving social cognitive deficits (29, 51–54). Importantly, cognitive neuroscience studies have identified DMN subsystems, anchored in part by distinct portions of the mPFC, that are involved in social processing (55). A dorsal mPFC subsystem—which shows strong connectivity with lateral cortex such as inferior frontal gyrus and temporoparietal junction—is involved in abstract social processing and mentalizing, whereas a ventral mPFC subsystem—tightly coupled with hippocampus and limbic regions—is involved in introspective thought driven by motivational and emotional states (56–58). These subsystems are believed to interact dynamically during successful social cognitive processing (57), and thus reductions in their interplay should be detrimental to social functioning. Moreover, the greater the positive (or weaker the negative) correlation between brain regions/networks has often been interpreted as reflecting a loss of network interplay [for a broader account of this functional "dedifferentiation" see, e.g., (59)]. Therefore, our findings may reflect emotion recognition failures associated with less differentiated activity of dorsal and ventral mPFC DMN subsystems, represented in our study by the dMPFC and parahippocampal cortex, respectively.

While a relationship between increased connectivity and reduced behavioral performance may at first seem counterintuitive, we highlight that such "hyperconnectivity" —particularly within the DMN—has been reported in several previous studies of moderate-severe TBI (60–65) as well as other neurologic disorders (66), although its functional significance has remained unclear. For example, it has been proposed that increased connectivity arises as an indirect response to structural disruption (61, 67), reflecting neural communication through alternative (and less efficient) pathways due to degraded direct connections [(68, 69); see (70), for review]. In this light, increased within-DMN connectivity may reflect a neural (but not necessarily behavioral) compensation for reduced structural integrity, arising from injury or from natural variation in white matter (14, 71, 72).

Lending further credence to the functional relevance of DMN RSFC to social processing, we noted that within-DMN connectivity was predictive of social integration of individuals with TBI. This complements recent schizophrenia research that demonstrates RSFC between DMN nodes is predictive of social functioning and competence (29, 30). Importantly, these relationships are not mediated by social or cognitive deficits, indicating that RSFC metrics may be *more* powerful predictors of social functioning outcomes than behavioral measures. These results suggest that DMN connectivity metrics may ultimately hold some promise as biomarkers relevant to clinical management and rehabilitation of TBI. Several studies have shown that functional connectivity has prognostic value in predicting recovery from brain injury (20, 73–76). Neuroimaging metrics can also be used to predict response to rehabilitative efforts: for instance, Arnemann et al. (77) found that functional network organization of individuals with acquired brain injury predicted their degree of improvement from a cognitive training intervention, implying that baseline neuroimaging could be used to identify individuals who are most appropriate for treatment. Furthermore, while still nascent in its clinical application—there is accumulating evidence that these neuroimaging metrics could themselves be the target of intervention, as demonstrated by the use of neurofeedback in EEG and real-time fMRI to rehabilitate brain injury (78, 79). The findings from the current study could thus have emergent clinical relevance in guiding treatment for TBI, particularly as it applies to social functioning and integration. Given the critical need for improving social functioning in TBI and the growing number of interventionist approaches which target social cognitive deficits (80, 81), results of the current study could inform this important subset of brain injury rehabilitation research: DMN connectivity could serve either as a predictor of treatment response to interventions, or as the treatment outcome itself.

The current study should be interpreted in the context of certain limitations. First, in contrast to many studies characterizing RSFC disruptions in TBI (82), we did not find significant connectivity differences between groups (as illustrated in **Figure 1**, the TBI group trended toward showing increased

frontal-temporal connectivity, but this was not significant). It is unclear whether this is attributable to the low power due to modest sample size (21 TBI), or to the difficulty in surviving multiple corrections due to the large number of regions in the DMN atlas we used for this study. However, in studies like ours which examine both group differences and individual differences, the regions that differ between TBI and HC are often not the same regions that covary with individual difference variables (e.g., 16, 66). Thus, the lack of significant group differences does not necessarily affect the interpretation of our individual difference findings. Another limitation from this study concerns its scope. Analyses from the current study were constrained to a single, theoretically motivated resting state network—the DMN. However, as the brain regions facilitating emotion recognition are not entirely limited to those found within the DMN (28), it is likely that our results would be more complex had we also examined other networks. For instance, Rigon et al. examined RSFC within a network of regions identified meta-analytically and found a distributed network (including intra- and inter-hemispheric connections) of frontal and temporal regions associated with emotion recognition ability in participants with TBI (16). Thus, while our results are not an exhaustive RSFC characterization of emotion recognition ability in healthy individuals or those with TBI, they provide a concise and theoretically informed illustration of the RSFC substrates of emotion recognition ability, and further demonstrate that these substrates can be used to predict social functioning in TBI.

CONCLUSION

We present the first evidence of RSFC correlates of emotion recognition within the DMN, and show that these metrics can be used to predict social functioning in individuals with moderate-severe TBI. These findings highlight the importance of examining intrinsic functional networks and their contributions to complex social processes and behavior.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Kessler Foundation Institutional Review Board.

AUTHOR CONTRIBUTIONS

HG and JL obtained grant funding to perform the study. All authors contributed to the study design, manuscript revision, and approved the submitted version. Data analysis was performed by KL and UV, and supervised by HG. The article was drafted by KL, UV, and HG.

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The Relationship Between Social Communication and Social Functioning in Pediatric TBI: A Pilot Study

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Objective: Social communication presents a significant difficulty for children with traumatic brain injury (TBI). Although several measures are used to examine social communication, there is no gold-standard assessment tool. The present pilot study examined the ability of the Social Communication Disorders Checklist (SCDC) to detect social communication difficulties in pediatric TBI. Further, we examined the relationship between social communication and social functioning as assessed by parental ratings of behavior and objective measures of social cognition.

Methods: Sixteen children with pediatric TBI and 20 age, education and sex matched healthy controls (HCs) participated. All participants participated in a neuropsychological evaluation and parents filled out questionnaires. Parents rated their children's social communication abilities using the SCDC, as well as the Behavior Assessment System for Children, Second Edition (BASC-2). The pediatric subjects completed a task of social cognition, specifically Theory of Mind (ToM).

Results: The pediatric TBI group had significantly lower scores on the SCDC compared to the HCs ($p = 0.001$). In the pediatric group, SCDC scores correlated significantly with scores on the BASC-2, as well as performance on the ToM task, indicating that children with lower parent-rated social communication abilities also had lower scores on the objective measure of social cognition.

Conclusions: These data provide preliminary evidence that children with TBI have difficulties with social communication, as evidenced by lower scores on the SCDC, and that SCDC scores correlate with subjective and objective measures of social cognition and behavior in pediatric TBI.

Keywords: pediatric, traumatic brain injury, social communication, social cognition, theory of mind

INTRODUCTION

Traumatic brain injury (TBI) that occurs during childhood results in cognitive, behavioral, emotional and social impairments (1–3). Such impairments can persist for years, even into adulthood (3–5). Pediatric survivors of TBI have significant impairments in "social functioning" (1, 2, 6), a term which refers to "the way an individual operates in a social environment by relying on social skills and interacting with others" (7). Impaired social functioning is associated with reduced well-being, academic performance and community integration (8, 9). Given its impact on other aspects of life, thorough investigation and assessment of social dysfunction in pediatric TBI is needed in clinical practice.

Social functioning can refer to a range of skills, including social or emotional perception, social cognition, social skills, social behavior, among others (7). One impairment particularly affected in persons with TBI is social communication. A recent meta-analysis indicated that a number of social communication skills are affected by pediatric TBI, including: taking-turns, maintaining a topic, discussion of appropriate topics, discourse organization, comprehension of contextual language (understanding ironic, deceptive or sarcastic language), perspective-taking, and understanding of non-verbal cues (10). Multiple theories of social functioning have suggested that social communication is also highly related to skills involving social cognition, including Theory of Mind (ToM) (7, 11, 12). ToM is the ability to understand the thoughts and beliefs of others, even when those thoughts/beliefs may not be obvious (such as the use of sarcasm). In the current study, we examined social communication in pediatric TBI utilizing the Social Communication Disorder Checklist [SCDC; (13)], and whether social communication assessed by the SCDC is related to social cognition, namely ToM.

Although social communication deficits have been studied extensively in pediatric TBI (10, 14–16), studies on social communication in pediatric TBI have relied on a number of varying measures, suggesting that there is no "gold-standard" for measuring this deficit (10). Many screening tools are cumbersome for parents to fill-out, and/or validated on a restricted age range [e.g., items on the La Trobe Social Problem Skills Inventory (17) may not be appropriate for younger children]. Thus, it has been suggested that more research is needed to accurately assess social communication in pediatric TBI, specifically examining possible screening tools (10). The SCDC is a unique measure that comprises the domains of (1) social reciprocity, (2) non-verbal skills (3) pragmatic language usage, and (4) behavioral impairments that affect interactions. It was developed as a quick and sensitive screening tool for autistic traits in children (13), as well as a measure of social communication abilities in clinical populations of attention-deficit-hyperactivity disorder (18) and oppositional defiant disorder (19). To date, however, its utility has not been examined in pediatric TBI.

In the current study, we sought to utilize the SCDC to examine social communication issues in pediatric TBI. The objective of the current study was to examine social communication using the SCDC to compare children with TBI to healthy controls (HC's). We examined whether difficulties quantified on the SCDC would be associated with parental ratings of other types of social functioning skills, such as those measured on the Behavior Assessment System for Children, Second Edition (BASC-2). Because the SCDC is a parent-report measure (and therefore subjective), we further investigated whether the SCDC was correlated with objective (non-self/parent report) measures of ToM: Ironic Criticism and Empathetic Praise task (ICEPT) a task which has been shown to be impaired in children with TBI. (11, 20). It was hypothesized that children with TBI who have more difficulty in social communication also have worse social cognitive abilities and social functioning.

MATERIALS AND METHODS

Participants

Participants included 16 children with a diagnosis of moderate-to-severe TBI. Injury severity was confirmed through parent-report in addition to a review of medical records. Specifically, diagnostic criteria included GCS scores (if available) of 8–12 (moderate), or <8 (severe), loss of consciousness (LOC) of >30 min (moderate) or >24 h (severe), as well as additional evidence of neurologic injury based on imaging (see **Table 1**).

Recruitment was achieved through Children's Specialized Hospital and through local neurology clinics. TBI participants were included if they were between the ages of 7 and 18, were at least 1 year post injury, and spoke English fluently. Participants were excluded based on a history of any neurological condition aside from the brain injury, a psychological disorder or learning disability diagnosed prior to the injury, or substance abuse. An additional 20 pediatric participants were included as HCs, and

TABLE 1 | Demographics in children with TBI and HCs and injury variables.

Demographics	TBI ($n = 16$)	HCs ($n = 20$)
Age (Mean ± SD)	11.56 ± 3.69	11.05 ± 3.11
Education (Mean ± SD)	6.19 ± 3.62	5.45 ± 3.07 years
Sex	11/16 Male	9/20 Male
Injury type		n/a
Motor Vehicle Accident (MVA)	12 (75%)	
Fall	1 (6.3%)	
Sports	2 (12.5)	
Abuse	1 (6.3%)	
Injury severity		n/a
Moderate	8 (50%)	
Severe	8 (50%)	
Months since injury		n/a
Mean (SD)	64.88 (44.28)	
GCS		n/a
Mean (SD)	6.43 (4.28)	
Positive for LOC	14 (87.5%)	n/a
Positive for imaging findings	12 (75%)	n/a

Education was defined in years (first grade completed = 1 year, second grade completed = 2 years, etc.); GCS, Glasgow Coma Scale; LOC, Loss of Consciousness.

were matched with TBI participants for age. The control group was recruited through local schools, or were relatives of those in the TBI group. There were no significant group differences found in education [$t_{(34)} = 0.66$, $p = 0.232$, $d = 0.22$ or age: $t_{(34)} = 0.45$, $p = 0.188$, $d = 0.15$] or sex between TBI and HC groups, $X^2 = 2.031$, $p = 0.154$. A summary of the demographic and injury specific variables is included in **Table 1**.

If participants in this study were 18 years old, they signed an informed consent approved by the Institutional Review Board of Kessler Foundation. If participants were minors, parents completed a consent for their child. All children were present during the consent process, and signed either a consent (children ages 13–17) or assent form (children ages 7–12). Compensation of $50 was provided to participants involved in this research.

Measures

Eligibility was first determined based on a parental phone screen, which detailed demographics, injury history, and related medical information. The measures used in this study were part of a larger battery completed by participants and their parents.

Social Functioning

Social Communication Disorders Checklist (SCDC)

Social Communication Disorders Checklist (SCDC) (13) was completed by parents/caregivers, and consisted of 12 items describing potential social communication skills of their child over the past six months. Parents rated how strongly the item applied to their child. The maximum score was 24, suggesting high social difficulties, while the lowest score was zero, or no noticed difficulties. The questions of the SCDC measure (1) social reciprocity (5 questions); (2) non-verbal skills (1 question); (3) pragmatic language usage (3 questions); and behavioral impairments that affect interactions (3 questions).

BASC-2

BASC-2 (21) is a standardized questionnaire used to assess skills, adaptive behaviors, and problematic behaviors or personality traits in children. The current study utilized the Parent Rating Scales (PRS)—Child (ages 6–11; PRS-C) and Parent Rating Scales—Adolescent (ages 12–21; PRS-A). Parents answered 160 questions for the PRS-C, or 150 questions for the PRS-A, indicating how frequently each behavior occurs in their child at home or in the community by rating it as "never," "sometimes," "often," or "always." For this study, we converted raw scores to T scores, and then created composite scores for each category: Externalizing Problems, Internalizing Problems, Behavioral Symptoms Index, and Adaptive Skills. Lower scores on all composite scores indicated less impairment, aside from Adaptive Skills in which a higher score indicates higher functioning in this area.

The Ironic Criticism and Empathetic Praise Task (ICEPT)

The Ironic Criticism and Empathetic Praise Task (ICEPT) (22) measures Theory of Mind, specifically, children's ability to recognize and interpret intentionality and inflection (22). ICEPT included 18 trials in which a scenario is described with a corresponding picture. In each scenario there was an image of an individual completing a task either poorly or well. There was also a second individual (the speaker) in each scenario who comments on how well the task was done. Participants were told the speaker's intentions (e.g., "He liked to cheer people up" or "He liked to bug and annoy people"). Participants then listened to a recording of the speaker telling the actor how well the task was done (e.g., "You did a great job tidying your room"). The inflection of the speaker's voice indicated whether the speaker was speaking literally (honestly), empathetically, or sarcastically. Participants were asked questions to assess story comprehension, as well as the ability to detect the beliefs (e.g., *"What did Jim think about the cake"),* and intentions *(e.g., "What did Jim want Betty to think about the cake"),* behind the speaker's comment. The dependent variables for ICEPT were the following for the current study: a total score (total items correct across all trials), a mastery score (children receive one point toward their Mastery Score for each story in which correct answers are given for all four belief and intention questions), total score for all belief questions, and total score for all intention questions. The IECPT has been shown to be impaired across multiple studies of pediatric TBI (11, 20, 22).

Statistical Analyses

Data analysis was conducted using Statistical Package for the Social Sciences for Windows, Version 21 (SPSS). Independent sample *t*-tests were used to compare TBI participants with HC participants on age, sex and education. To examine group differences between the TBI and HC groups on the SCDC, ICEPT, and the BASC-2, multivariate analyses of variance were run. Because the age range was broad in the current sample, and because social communication and social cognition is affected by development, we include age as a covariate. One child in the pediatric TBI group did not complete the BASC-2 due to time constraints during testing session. Pearson correlations were run to examine the relationship between SCDC and all other social functioning measures in the TBI group only, as our research question was specific to the TBI group. As age of injury is likely a confounding variable, we also performed partial correlations, controlling for age of injury.

RESULTS

Group Differences on SCDC, BASC-2, and ICEPT

Group differences are summarized in **Table 2**. On the SCDC, parents of children with TBI rated their children as having significantly higher social communication problems compared to HCs ($p < 0.001$). According to parental ratings on the BASC-2, the pediatric TBI group had significantly higher Externalizing Problems Composite scores (assessing hyperactivity, aggression, and conduct problems) compared to the HC group ($p = 0.009$). The pediatric TBI group also had significantly higher scores on the Internalizing Problems Composite Score (assessing anxiety, depression, and somatization) compared to HCs ($p = 0.011$). The pediatric TBI group had significantly higher scores on the Behavioral Symptoms Index (assessing atypicality,

TABLE 2 | Group differences on tasks of social functioning.

	TBI $n = 16$ (15 for BASC)	HC $n = 20$	F	p-value	Partial eta squared
SCDC	9.69 (6.44)	0.65 (1.14)	48.72	0.000*	0.604
BASC externalizing	55.67 (16.24)	42.70 (5.14)	12.15	0.001*	0.275
BASC internalizing	58.13 (18.98)	43.60 (6.20)	10.84	0.002*	0.253
BASC behavioral	60.33 (17.06)	41.50 (4.83)	24.24	0.000*	0.431
BASC adaptive skills	39.80 (9.07)	58.60 (7.10)	29.25	0.000*	0.478
ICEPT correct	142.13 (32.35)	171.55 (18.08)	15.50	0.000*	0.326
ICEPT mastery	9.31 (5.70)	14.70 (3.77)	17.11	0.000*	0.348
ICEPT belief	45.31 (19.10)	61.30 (9.92)	11.18	0.002*	0.259
ICEPT intent	44.94 (17.23)	56.40 (11.47)	7.96	0.008*	0.199

SCDC, Social Communication Disorders Checklist; BASC-2, Behavior Assessment System for Children, Second Edition; ICEPT, Ironic Criticism and Empathetic Praise task.
**Significance levels of < 0.01.*

withdrawal, and attention problems) compared to HCs, $p = 0.001$. The pediatric TBI group had significantly lower scores on the Adaptive Skills Composite (assessing adaptability, social skills, leadership, activities of daily living, and functional communication) compared to HCs, $p < 0.001$.

In terms of social cognition, the pediatric TBI group showed significant impairments relative to HCs on ICEPT, in terms of total score, $p = 0.004$, mastery scores, $p = 0.003$, all belief questions, $p = 0.006$, and all intentions questions, $p = 0.023$.

Association Between SCDC and Subjective/Objective Measures of Social Functioning

Pearson correlations revealed that parental rating on the SCDC was correlated positively with all composite scores of the BASC-2 PRS for the pediatric TBI group: Externalizing Problems Composite [$r_{(15)} = 0.66$, $p = 0.004$, Internalizing Problems Composite [$r_{(15)} = 0.53$, $p = 0.022$], Behavioral Symptoms Index [$r_{(15)} = 0.77$, $p < 0.001$], and negatively with Adaptive Skills Composite [$r_{(15)} = -0.76$, $p < 0.001$]. These correlations indicate that parents who rated their children as having worse social communication abilities rated their children as having more behavioral and social concerns on BASC-2. Partial correlations, controlling of age since injury were consistent with bivariate correlations: SCDC scores correlated with Externalizing Problems Composite ($r_{partial} = 0.63$, $p = 0.008$), Internalizing Problems Composite ($r_{partial} = 0.50$, $p = 0.035$), Behavioral Symptoms Index ($r_{partial} = 0.75$, $p < 0.001$), and negatively with Adaptive Skills Composite ($r_{partial} = -0.64$, $p < 0.007$).

Related to the ICEPT task, Pearson correlations revealed that the SCDC total score was negatively correlated with the following ICEPT variables: total correct on all ICEPT questions, [$r_{(16)} = -0.54$, $p = 0.016$], ICEPT Mastery Score, [$r_{(16)} = -0.55$, $p = 0.014$], total intention questions, [$r_{(16)} = -0.61$, $p = 0.006$]. Bivariate correlations were largely consistent with the partial correlations, which revealed SCDC correlated with total correct on the same ICEPT questions, even after controlling for age of injury [$r_{partial}$ $(16) = -0.49$, $p = 0.038$], ICEPT Mastery Score, [$r_{partial}$ $(16) = -0.48$, $p = 0.041$], total intention questions, [$r_{partial}$ $(16) = -0.58$, $p = 0.015$].

DISCUSSION

This pilot study examined social communication deficits in pediatric TBI using the SCDC, and investigated whether parent-reported difficulties in SCDC correlate with other measures of social functioning. The results showed that children with TBI have significantly lower social communication compared to HCs, offering preliminary evidence that the SCDC is able to detect these deficits in pediatric TBI. Further, the SCDC scores in children with TBI were correlated with both subjective and objective measures of social functioning and social cognition. The SCDC is a tool to assess children with autism spectrum disorder (ASD) (13, 23, 24), as well as autistic traits in the general population (25). The results of this study suggest that the SCDC may have clinical utility in children with TBI.

A number of questionnaires have been used to assess social communication impairments following pediatric TBI including the La Trobe communication questionnaire (17), the social problem solving skills inventory—revised (26) and the social skills rating scale (27). However, while these measures have been shown to be able to detect social communication impairments in TBI, we propose that the SCDC may hold some benefit over them. While some social communication measures can have as many as 57 items and take as much as 45–60 min to fill out, the SCDC is a short assessment tool with only 12 items. Thus, it can be used as a screening tool for clinicians as it is not cumbersome for parents and can be completed quickly. Utilization of such a tool would better guide clinicians to develop treatment plans incorporating ways to improve social communication (i.e., social skills therapy or metacognitive therapy) (28–30). Due to the preliminary nature of the current study and the small sample size, the findings should be interpreted with caution. More research is needed on the utility of the SCDC in pediatric TBI, including examination of psychometric properties, in order for it to be recommended as a screening tool.

The current study examined whether parental ratings of social communication assessed with SCDC were related to either subjective or objective measures of social function and social cognition. On the BASC-2, children with TBI were rated by their parents as having more behavioral and social issues compared to HCs. Further, BASC-2 ratings were significantly correlated with the SCDC ratings. As the BASC-2 assesses social

functioning (including some elements of social communication), the correlation between these two measures suggests a level of convergent validity that should be confirmed with a larger sample in a psychometric study designed to test the validity of the SCDC in pediatric TBI.

As both the BASC-2 and the SCDC are based on parental report and therefore subjective in nature, the current study included a task of ToM to investigate how SCDC scores were related to objective measures of social cognition. Children with poor ToM skills, evidenced by reduced performance on ICEPT, also had reduced social communication skills. Impairments in ToM may make it difficult for some to understand the beliefs/thoughts of others, which may further lead to inappropriate social communication/behavior. In line with this, the recently postulated socio-cognitive integration of abilities model (SOCIAL) suggests that social cognitive abilities (emotion perception) can affect social skills/function, taking into account mediating factors such as brain development/health, socioeconomic status and culture (7). This model also suggests that social cognitive impairments specifically may be associated with reduced social functioning, as opposed to general cognitive abilities. The results of the current study are in line with this model in pediatric TBI.

A further possibility explaining the relationship between social communication and social cognitive abilities is that the relationship between the two deficits are due to a direct consequence of brain injury affecting neural networks responsible for both social communication deficits and ToM. Consistent with this, studies have shown that reduced integrity of the corpus callosum following pediatric TBI is associated with both ToM deficits and social communication difficulties (31). Thus, as brain regions responsible for multiple aspects of social functioning are damaged following TBI, deficits in both social communication and social cognition may occur (32). Future studies combining structural and functional neuroimaging with measures of social cognition and social communication will further elucidate the neural networks underlying these separate areas of social functioning.

A third possibility to explain the relationship between social cognition and social communication is related to the development of social functioning skills in pediatric TBI. Longitudinal studies have shown that social functioning deficits persist for years following a TBI (3, 33, 34). An injury early on in life (e.g., infancy) may have lasting effects on the social brain, especially on social perception skills which develop in infancy (ToM). However, the later development of social communication skills may be affected because either brain regions which were injured may not develop properly or the needed social cognition skills are not present at the time of communication development. Further, other factors related to social skills development may influence social communication. For example, social isolation and reduced friendship has been observed in children with TBI (35). It can be argued that a child who is socially isolated would have reduced ability to practice/develop social communication skills. At this point, future studies examining the longitudinal development of social skills over time in pediatric TBI are needed to examine whether factors such as social isolation affect social communication development.

The current study was limited by a small sample size. A larger sample size would allow for the comparison between TBI severity groups and to adequately examine the psychometric properties of the SCDC in pediatric TBI. More rigorous analyses of psychometric properties would potentially allow for recommendation of the SCDC to be utilized as a clinical screening tool. Additionally, a larger sample would enable us to perform analyses which would indicate whether the SCDC ratings predicted social communication impairments identified in a more comprehensive evaluation with standardized measures. Further, the lack of neuroimaging data does not enable examination of neural networks underlying social communication deficits in pediatric TBI. Thus, future studies combining imaging with SCDC will allow for better understanding of how certain TBI-related injuries, such as diffuse axonal injury, are related to social communication skills.

In conclusion, the present results demonstrate that children with TBI are impaired in social communication as indicated by the SCDC. As the SCDC was designed to examine deficits in ASD, these findings indicate a behavioral overlap between pediatric TBI and ASD that should be further explored. Furthermore, social communication was associated with an objective task of social cognition (ToM), supporting theoretical models that social communication is highly related to social cognition. While the current sample size precludes us from making any definitive conclusions, this study may indicate that the SCDC is a tool which can be utilized in TBI to examine social communication. Future studies should be conducted which are more highly powered to examine the psychometric properties of this task in pediatric TBI.

DATA AVAILABILITY

The datasets generated for this study are available upon request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the institution review board (IRB) of Kessler Foundation with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Kessler Foundation IRB.

AUTHOR CONTRIBUTIONS

HG conceptualized the study design. HG and AH wrote the first draft of the manuscript and performed statistical analysis. AH organized the database and tested subjects. HG, AH, JN, JD, and JL wrote sections of the manuscript. All authors provided editorial comments and approved the submitted version.

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Neurobehavioral Symptoms in Community-Dwelling Adults With and Without Chronic Traumatic Brain Injury: Differences by Age, Gender, Education, and Health Condition

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Neurobehavioral symptoms after Traumatic Brain Injury (TBI) are prevalent, persist for many years, and negatively affect long-term health, function, and quality of life. Symptoms may differ based on age, gender, education, race, ethnicity, and injury severity. To better understand neurobehavioral functioning after TBI, we need a comprehensive picture of emotional, cognitive, and behavioral symptoms in the context of personal factors that may affect these symptoms. We also need to understand the extent to which these symptoms are specific to TBI, shared across other neurological conditions, or attributable to factors outside of the injury itself. We collected neurobehavioral symptoms via the self-reported Behavioral Assessment Screening Tool (BAST) in a National Cohort of English (n = 2,511) and Spanish speaking (n = 350) community-dwelling adults with and without chronic TBI and other neurological and mental health conditions. The primary focus of the present study was to comprehensively describe neurobehavioral symptoms in adults with and without TBI, broken down by gender and health conditions and then further by age group or educational attainment. As expected, participants with TBI reported more symptoms than Healthy Controls. Regardless of condition, women reported more fatigue, while men reported more substance abuse and impulsivity. Hispanic participants reported more neurobehavioral symptoms than non-Hispanic participants did across health conditions, though primarily Spanish-speakers reported fewer symptoms than English-speakers, suggesting that level of acculturation may contribute to symptom reporting. These data provide a comprehensive characterization of neurobehavioral symptoms in adults with TBI and adults without TBI (healthy controls, adults with other neurological conditions, and adults with mental health conditions).

Keywords: traumatic brain injury, behavior, emotion, gender, age, education

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INTRODUCTION

Following Traumatic Brain Injury (TBI), emotional and behavioral symptoms are prevalent, often persist for many years, and negatively affect long-term health, function, and quality of life (1–7). Neurobehavioral symptoms, including aggression, disinhibition, lack of motivation, and planning/executing actions (8, 9), are among the greatest contributing factors to poor outcomes

after TBI (e.g., disability, depression, suicidality, quality of life) (5, 10, 11). The extent to which neurobehavioral symptoms in chronic TBI result from the injury itself or are due to other factors, such as personal characteristics or comorbid neurological or mental conditions remains unclear. Neurobehavioral symptoms are more likely to occur in the context of chronic emotional disruptions [e.g., depression (12–15)] that are common in the general population and after TBI (16, 17). Symptom-reporting after injury may also differ based on age (18, 19), gender (20, 21), education (22), race or ethnicity (23), and injury severity (24, 25), though differences in symptom reporting by these personal factors are present in other clinical populations and the general population as well. A nationwide epidemiological study on TBI-related emergency department visits concluded that many of the common neurobehavioral symptoms after TBI may be more related to pre-existing psychiatric conditions (e.g., post-traumatic stress disorders, substance use disorders) and personality features (e.g., impulse control problems, high-risk behaviors) that put an individual at greater risk for sustaining a TBI, rather than to just the injury itself (17). Similarly, a recent study on chronic traumatic encephalopathy (CTE) found that many of the clinical symptoms used to diagnose CTE, including mood, emotional regulation, and behavioral symptoms, were also common in men with depression in the general population, indicating that these symptoms are not necessarily specific to brain pathology (26). To better understand neurobehavioral functioning after TBI, we need a comprehensive and concurrent picture of emotional, cognitive, and behavioral symptoms in the context of personal factors and health conditions that may affect these symptoms.

Age

The extent to which age-related differences in neurobehavioral symptoms are specific to TBI or attributable only to age effects remains unclear. Psychiatric symptoms appear to occur more often in younger adults, whereas fatigue and other physiological symptoms appear to be more common in older adults, both in the general population and among those with TBI. One study reported that adults under 65 years old with TBI more often had psychiatric diagnoses compared to those over 65 with TBI (19), consistent with the pattern of psychiatric diagnoses by age observed in the general population (27, 28). Breed et al. (18) compared injury severity-matched older and younger adults with TBI and age-matched healthy controls on a number of self-reported symptoms. They found that younger adults (18–35 years) with TBI reported more sleep difficulties than older adults with TBI (over 55) and age-matched controls. Older adults with TBI reported more fatigue-related symptoms and more neurologic symptoms, such as headaches, seizures, and difficulties producing and understanding speech, than age-matched peers without TBI (18). Despite similar main effects of age on symptom-reporting, experiencing a TBI does seems to exacerbate problems related to sleep and neurologic symptoms.

Gender

Psychiatric and neurobehavioral symptoms are more prominent in women than men, both in the general population and after TBI. Women report more symptoms of depression, anxiety, fatigue, and, in some studies, sleep disturbances following TBI (20, 21). Men report more restlessness, more difficulty setting realistic goals, and in some studies more sleep disturbances than women after TBI (21). A review of the literature reveals similar patterns within the general population as well, with higher rates of depression and subsequent fatigue and anxiety among women compared to men (29). One study on gender differences in executive function post-TBI found that women had better executive functioning than men, even after controlling for education and ethnicity (30). In the general population, men are more prone to impulsive behaviors (31, 32). but women may be more likely to report impulsivity symptoms when they are present (31). Further, the relationship between impulsivity and substance abuse may differ as a function of gender, with a stronger association among women than men (32). Notably, despite a growing acceptance that gender is not a binary construct, the literature on gender differences after TBI fails to represent genders outside of men and women.

Education

The relationship between educational attainment and mental health symptoms is complicated. Prior research in the general population in Sweden demonstrated a negative correlation between mental health issues during childhood and ultimate educational attainment (33), suggesting that a predisposition to poorer mental health early in life may negatively impact education level later in life. A study on a nationally representative sample of non-institutionalized adults in the United States found that those with lower levels of education reported higher rates of depressive symptoms, lower rates of treatment, and greater likelihood of increasing depressive symptoms over time (34). Similarly, a longitudinal study by Dikmen et al. (22) found that individuals without a high school degree had greater depressive symptoms than those with at least a high school degree, 1-year post-TBI. The authors suggested that these individuals may have fewer resources to help cope with the injury, as well as greater difficulty in returning to work (22). In both the general population and TBI, the adverse effects of lower education may be more prominent in individuals from disadvantaged vs. advantaged backgrounds (35–37).

Race and Ethnicity

Racial and ethnic minority groups, particularly Hispanic individuals, are at greater risk for sustaining a TBI (38) and report more psychiatric symptoms, physical limitations, and cognitive deficits following TBI compared to non-Hispanic white individuals (23, 39–41). Racial and ethnic minorities also frequently experience health care disparities (23, 39–41) that magnify the long-term consequences of TBI (37, 39, 41–46). In contrast, Hispanic and black individuals within the general population are less likely than non-Hispanic white individuals to report a psychiatric diagnosis (47). Research on the effects of race and ethnicity on neurobehavioral symptoms is therefore complicated by potential differences in symptom experience vs. differences in symptom reporting.

TBI Injury Severity: Mild vs. Moderate-Severe

Chronic neurobehavioral symptoms after TBI can occur across all levels of injury severity (1–7). Moderate-to-severe TBI may have a larger physiological and cognitive impact, but greater self-awareness and less obvious disability following a mild TBI, as compared to moderate-to-severe TBI, may lead to more emotional distress and subsequent reporting of stress and depressive symptoms (48). In a study on combat-related TBI, individuals with mild TBI endorsed more posttraumatic stress and post-concussive symptoms than those with moderate-to-severe TBI, even after controlling for age, time since injury, and mechanism of injury (24). However, after controlling for posttraumatic stress symptoms, there were no differences in post-concussive symptoms, leading the authors to suggest that greater post-concussive symptom-reporting was a function of emotional distress rather than injury severity (24). Examining differential patterns in neurobehavioral symptoms as a function of injury severity may improve targeted intervention.

To date, research looking across injury severity and across factors known to impact neurobehavioral symptoms post-TBI is limited. Though Breed et al. compared symptom reporting between older and younger individuals with TBI to each other and to age-matched healthy controls, they focused on physical symptoms rather than neurobehavioral and emotional consequences of brain injury (18). Holzer et al., in a recent epidemiological study in TBI, specifically identify a need for more research to examine the interplay between TBI and both psychiatric and personality-related factors to better understand post-injury neurobehavioral symptoms (17). No one has directly compared neurobehavioral symptoms in healthy controls vs. those with TBI, nor has anyone compared individuals with TBI to individuals with other neurological or mental health conditions commonly co-occurring with TBI that could explain post-injury neurobehavioral symptoms. It is currently unclear if these neurobehavioral symptoms, seen post-TBI, are due to brain injury itself, an increased risk for neurological and/or mental condition(s) predating or following TBI, or a combination of these factors. Furthermore, despite the growing proportion of Spanish-speaking adults in the United States (49), these individuals are often excluded from research on chronic TBI (43).

The current study presents a neurobehavioral characterization from a nationally representative sample of individuals with TBI across levels of injury severity and individuals without TBI, both with and without other neurological or mental health conditions. We used a patient-reported outcome measure of neurobehavioral symptoms, the BAST, to capture multiple dimensions of neurobehavioral function. We examined differences in neurobehavioral symptoms across health condition groups (healthy controls, mild TBI, moderate-severe TBI, history of other neurological conditions, and history of mental health conditions). We then examined neurobehavioral symptoms within each health condition group by gender and age or education. We also explored differences based on ethnicity and primary language. This study thoroughly characterizes neurobehavioral symptoms common after TBI and provides comparative data in both English- and Spanish-speaking healthy controls, individuals with TBI, and individuals with other neurological and/or mental health conditions, both for future studies and for clinical practice.

MATERIALS AND METHODS

Setting

We collected self-reported neurobehavioral symptoms electronically via Qualtrics™ in a nation-wide survey study of community-dwelling adults with and without TBI.

Participants

Participants were adults (>18 years old), fluent in either English or Spanish, with no self-reported history of schizophrenia or dementia, who electronically consented to participate. For the purposes of this study, we separated those who took the survey in English and those who took the survey in Spanish into two distinct cohorts.

Procedures

We created an electronic survey of the BAST using Qualtrics™ (Qualtrics, Provo, UT) HIPAA-compliant survey platform, to collect data from a national sample from both the general population and those with self-reported lifetime history of TBI. We established sampling quotas based on: (1) age and gender distributions generally observed in TBI; (2) BAST language (English or Spanish); and (3) presence or absence of self-reported history of TBI or concussion. Qualtrics serves as a survey panel aggregator, leveraging multiple survey companies to send out electronic requests for participants willing to complete a survey study. Through this service, we obtained electronic survey responses meeting our sampling quotas. Qualtrics automatically removed survey responses completed in <1/3 of the median time it took the first 150 participants to complete the survey. Our study team conducted further data checks on all surveys, with Qualtrics removing and replacing surveys deemed invalid by the study team. Determination of invalidity was based on gibberish in open-text responses, illogical responses (e.g., endorsing never feeling fatigue and always limiting physical activities because of fatigue), questionable open-text responses with other evidence that responses were invalid (e.g., duration of the total survey, validity checks, inconsistency in answers), and the two validity items embedded in the BAST. Though we do not have data on how many potential participants received an invitation to take the survey, nor how many Qualtrics automatically removed as a part of their internal validity check, we tracked all survey responses we received and reasons for deeming surveys ineligible. Qualtrics removed and replaced $n = 558$ invalid responses over the course of 12 separate data quality checks conducted by study investigators. Further data quality checks after the survey was close resulted in removal of an additional $n = 202$ invalid responses, the majority ($n = 164$) due to the survey being taken in English by non-fluent native Spanish speakers (open-ended responses provided in Spanish). We confirmed TBI presence and severity with an electronic version of a structured questionnaire modeled after the OSU-TBI (50). Capturing these data via structured electronic

questionnaire has demonstrated validity in a prior study in a TBI sample (51). We then generated a map of all responses to show national representation of the study cohort, depicted in **Figure 1**.

Measures

A demographic questionnaire captured age, gender, race, ethnicity, highest level of education completed, native language, and history of various health conditions. Based on the health conditions selected, participants were either excluded (dementia, schizophrenia) or categorized as:

- Healthy Controls (selecting "none of the above")
- Other Neuro Conditions (selecting any of the following: learning disability, ADHD, Stroke, Multiple Sclerosis, Parkinson's Disease, Autoimmune condition, Other neurological condition)
- Mental Health Conditions only (selecting only one or more of the following: Post-traumatic stress disorder, Bipolar disorder, depression, anxiety, alcohol abuse/dependence, drug abuse/dependence, other mental health condition)
- TBI (selecting Traumatic Brain Injury or Concussion). Those categorized in the TBI group also completed a questionnaire following the structure and content of the OSU-TBI, to confirm history of TBI and to classify injury severity. The OSU-TBI Worst Injury Score ranges from 1 to 5, with 1 indicating no history of TBI, 2 and 3 indicating mild TBI, 4 indicating moderate TBI, and 5 indicating severe TBI (50). These scores classified participants' injuries as Mild or Moderate-Severe. This includes any lifetime history of TBI (e.g., during childhood or adulthood).

Participants selected their preferred language for completing the survey (English or Spanish), and all subsequent questionnaires were presented in their preferred language.

Behavioral Assessment Screening Tool (BAST)

Effectively measuring neurobehavioral symptoms in community-dwelling populations is challenging, but necessary for valid and clinically relevant characterization and interpretation to inform problem-identification and treatment. The Behavioral Assessment Screening Tool (BAST) is a self-reported neurobehavioral symptom measure developed based on a theoretical model that frames behavior as an overarching concept with multiple interacting domains, including emotions, cognitive function, and personal factors, all in the context of individuals' existing environmental supports and stressors (52). It employs simple language and sentence structure at the 8–9th grade reading level in both English and Spanish, includes items specifically assessing validity of responses, and has a validated multidimensional structure to cover the complexity of neurobehavioral symptoms after TBI (53–55). We developed the Spanish-language version through both translation and language validation, including a language validation committee and cognitive interviewing (55).

The BAST, in both English and Spanish, measures self-reported neurobehavioral symptoms in five domains: Negative Affect, Fatigue, Substance Abuse, Executive Function, and Impulsivity. It demonstrates good content validity and a multidimensional factor structure with good internal consistency reliabilities (Cronbach's alpha's ranging from $\alpha = 0.76$–0.90) (54) among community-dwelling adults with chronic TBI (53, 54). To create comparable scores for each subscale, we summed the individual item scores and divided by the total number of items within each subscale; this yielded an average subscale score ranging from 1 to 5, with one indicating never experiencing that symptom and 5 indicating experiencing that symptom very often. Of note, though the BAST was developed and initially validated in chronic TBI, none of the symptoms is specific to brain injury, nor is any attribution made as to the etiology of the symptoms. The purpose of the BAST is screening for problematic neurobehavioral symptoms that may negatively affect individuals' health and well-being, regardless of etiology. However, as no one has yet validated the BAST in adults without TBI, we present Cronbach's α for each of the subscales within each cohort as a measure of the BAST's reliability in non-TBI samples. Cronbach's α's can be interpreted as follows: >0.70 = Acceptable, >0.80 = Good, >0.90 = Excellent.

Analyses

We calculated frequency and percentages to characterize each health condition group and means with standard deviations for each of the BAST subscales to characterize neurobehavioral symptoms. BAST subscale average scores were computed by summing scores on subscale items and dividing by the total number of items, which yielded comparable scores ranging from 1 (never) to 5 (very often) for each subscale. We present descriptive data broken down by gender and health conditions and then further by either age group or educational attainment among primary English speakers and primary Spanish speakers, separately. We also compared BAST subscale scores within each health by ethnicity and primary language. We used non-parametric tests for independent samples (Kruskal-Wallis, Mann-Whitney) for all comparisons. All analyses were performed using Statistical Packages for the Social Sciences (SPSS, v.24) software with a conservative overall significance level of $\alpha = 0.01$ to account for multiple testing and an adjusted alpha = 0.003 for *post hoc* testing.

RESULTS

Participants

After completing all validity checks, we retained 2,511 complete BAST surveys in English ($n = 2{,}461$ were native English-speakers, 50 were native Spanish-speakers fluent in English), of which $n = 2{,}248$ reported no TBI history, $n = 211$ reported Mild TBI, and $n = 52$ reported Moderate-Severe TBI. For those with no history of TBI ($n = 2{,}248$), we further broke down the cohort into those with no self-reported history of neurological or mental health condition; (Healthy Controls; $n = 1{,}548$), neurologically healthy controls with *only* a self-reported history of a mental health condition (Mental Health Conditions; $n = 427$), and

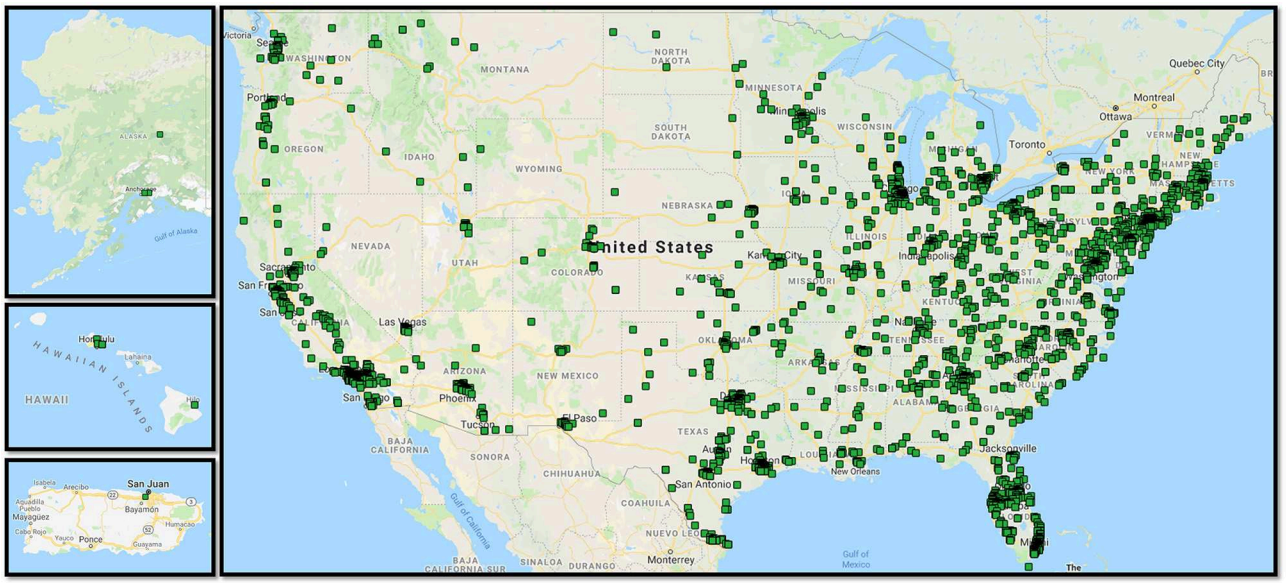

FIGURE 1 | Mapped survey responses for the National cohort study. Map made using BatchGeo (http://batchgeo.com/).

controls who reported *any* history of another neurological condition (Other Neuro Conditions; $n = 273$). **Table 1** presents demographic and neurobehavioral symptom data by group for all participants taking the survey in English.

We retained 350 complete BAST surveys in Spanish, of which $n = 11$ reported a history of Mild-Severe TBI, $n = 296$ were Healthy Controls, $n = 27$ had only Mental Health Conditions, and $n = 16$ had Other Neuro Conditions. **Table 3** presents demographic and neurobehavioral symptom data by group for primarily Spanish-speaking participants.

Neurobehavioral Symptoms

Neurobehavioral symptoms broken down by gender and condition for each subscale are further broken down by age group or by educational attainment in **Table 2** for English-speaking participants. Numbers of participants in each cell of **Table 2** are available in **Supplemental Table A**. For primarily Spanish-speaking participants, **Table 3** presents neurobehavioral symptoms separately by condition and **Table 4** presents neurobehavioral symptoms broken down by gender or educational attainment within each health condition group.

Cronbach's alphas within each cohort and by health condition, presented in **Table 5**, indicate that the BAST subscales overall demonstrated acceptable to excellent internal consistency reliabilities across all cohorts and health conditions ($\alpha = 0.70$–0.92), with a few exceptions falling just below acceptable ($\alpha = 0.61$–0.69). One notable anomaly for primarily Spanish speakers was the Impulsivity subscale, which had a Cronbach's $\alpha = 0.48$, potentially due to the very small sample size ($n = 11$) and limited variability in this group. We will evaluate item properties in the future in a larger sample.

Group Comparisons

Gender Differences by Health Condition Within Each Cohort

Table 6 summarizes differences in neurobehavioral symptoms between men and women by health condition within each cohort. Note that most gender differences occurred among English-speakers. Overall, men had significantly higher Substance Abuse and Impulsivity scores while women had higher Fatigue scores.

Educational Attainment Differences by Health Condition Within Each Cohort

Regarding differences in neurobehavioral symptoms between participants with less than or equal to a High School education and participants with some post-secondary training (>High School) by health condition, healthy controls with some post-secondary training had significantly better Executive Function ($p < 0.001$) in both English and Spanish-speakers. English-speaking healthy controls with some post-secondary training also had fewer Impulsivity symptoms ($p < 0.001$). There were no statistically significant differences in neurobehavioral symptoms by educational attainment in any of the Mental Health, Other Neuro, or TBI groups.

Language and Ethnicity Differences by Health Condition

Within the healthy control group, English-speakers had significantly higher scores for Substance Abuse ($p < 0.001$) than did Spanish-speakers; however, within the mild-severe TBI health condition, Spanish-speakers reported significantly higher neurobehavioral symptoms for Executive Function and Impulsivity ($p < 0.001$) than did English-speakers. In the full cohort, combining English- and Spanish-speakers, we

TABLE 1 | Demographics and neurobehavioral symptoms in English-speaking community-dwelling adults with and without TBI.

Participant characteristics		English-speaking national cohort ($n = 2511$)				
		Mild TBI $n = 211$ *n* (%)	**Moderate-severe TBI** $n = 52$ *n* (%)	**Healthy controls** $n = 1548$ *n* (%)	**Mental health conditions** $n = 427$ *n* (%)	**Other neuro conditions** $n = 273$ *n* (%)
Gender	Women	114 (54.0%)	20 (38.5%)	544 (35.1%)	225 (52.7%)	137 (50.2%)
	Men	92 (43.6%)	30 (57.7%)	998 (64.5%)	196 (45.9%)	130 (47.6%)
	Transgender/other	5 (2.4%)	2 (3.8%)	6 (0.4%)	6 (1.4%)	6 (2.2%)
Race	White	180 (85.3%)	39 (75.0%)	1104 (71.4%)	321 (74.2%)	210 (77.0)%
	Black/African American	11 (5.2%)	4 (7.7%)	181 (11.7%)	43 (10.1%)	23 (8.5%)
	Asian	6 (2.8%)	5 (9.6%)	50 (3.3%)	9 (2.1%)	10 (3.7%)
	American Indian/Alaskan Native	4 (1.9%)	1 (1.9%)	21 (1.4%)	7 (1.6%)	3 (1.1%)
	Native Hawaiian/Pacific Islander	1 (0.5%)	2 (3.8%)	6 (0.4%)	1 (0.2%)	2 (0.7%)
	Other	7 (3.3%)	1 (1.9%)	172 (11.2%)	43 (10.2%)	20 (7.3%)
	Unknown	2 (0.9%)	0 (0%)	13 (0.8%)	3 (0.7%)	5 (1.8%)
Ethnicity	Hispanic	23 (10.9%)	6 (11.5%)	448 (30.0%)	114 (26.7%)	57 (20.9%)
	Non-hispanic	183 (86.7%)	46 (88.5%)	1,046 (67.6%)	307 (71.9%)	209 (76.6%)
	Unknown	5 (2.4%)	0 (0%)	54 (3.5%)	6 (1.4%)	7 (2.6%)
Education	≤High school	37 (17.5%)	9 (17.3%)	466 (30.1%)	158 (37.0%)	112 (41.0%)
	>High school	174 (82.5%)	43 (88.5%)	1,082 (69.9%)	269 (63.0%)	161 (59.0%)
		Mean (*SD*)	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**
Age (years)		40.55 (15.50)	44.15 (15.72)	44.55 (17.73)	39.58 (15.15)	37.45 (14.73)
Range		18–81	21–82	18–90	18–86	18–78
BAST subscales	Negative affect	3.26 (0.75)	3.16 (0.69)	2.55 (0.61)	3.34 (0.68)	3.26 (0.69)
	Fatigue	3.16 (0.89)	3.07 (0.70)	2.40 (0.70)	3.15 (0.80)	3.14 (0.76)
	Executive function	2.27 (0.66)	2.40 (0.68)	2.05 (0.52)	2.32 (0.58)	2.37 (0.57)
	Impulsivity	2.30 (0.75)	2.44 (0.82)	2.04 (0.69)	2.41 (0.81)	2.43 (0.76)
	Substance abuse	1.83 (0.94)	2.10 (1.03)	1.43 (0.67)	1.81 (0.96)	1.72 (0.93)

All BAST Subscale values are mean (standard deviation) of the average score across items in each subscale.
Color values in the tables are to allow for comparison across tables of BAST subscales. Purple, negative affect; Green, fatigue; Blue, executive function; Red, impulsivity; Yellow, substance abuse.

ran exploratory analyses to identify any differences within condition based on ethnicity (Hispanic vs. Non-Hispanic) and based on native language and survey language of the participant. The three language groups were English speakers taking the survey in English (E), native Spanish speakers taking the survey in English (SE; confirmed English fluency via responses to open-ended questions), and Spanish speakers reporting in Spanish (SS). **Table 7** summarizes the statistically significant findings from all exploratory analyses. We found significant differences in Impulsivity and Executive Function between ethnicity groups in both healthy controls and those with mild-severe TBI. Other notable differences between ethnicity groups included Negative Affect in healthy controls. For all significant comparisons, Hispanic participants reported more frequent symptoms than non-Hispanic participants did. We also observed significant differences between language groups. In healthy controls, native English speakers reported more Fatigue, Impulsivity, and Substance Abuse than primarily Spanish speakers. In those with TBI, primarily Spanish speakers reported more Impulsivity than English speakers did. Native Spanish speakers taking the survey in English did not differ from either other language group in any condition.

DISCUSSION

Practitioners and researchers alike widely accept that neurobehavioral symptoms exist and persist after TBI, but debate still ensues as to symptom etiology. Brain injury itself leads to neurobehavioral problems, but comorbid neurological and mental health conditions, as well as gender, age, and other demographic factors all likely contribute to symptom development and chronicity after TBI as well. Additionally, neurobehavioral symptoms themselves are heterogeneous, incorporating multiple interacting domains, including emotion, cognition, and environmental supports and stressors. To address the variety of factors contributing to multifaceted neurobehavioral symptoms common after TBI and other neurological and mental health conditions, we employed a multidimensional behavioral symptom measure—the BAST—and reported differences in symptom profiles between individuals with various neurological and mental health conditions broken down by gender, age, education, and ethnicity.

The BAST yielded higher scores in TBI than in healthy controls, as expected, which supports its content validity, even in diverse samples. However, individuals with other neurological conditions or with mental health conditions also reported more

TABLE 2 | Neurobehavioral symptoms by gender, neurological and mental health conditions, age, and education among English-speakers.

BAST subscale	Age (years)	Women					Men				
		Mild TBI	Moderate-severe TBI	Healthy controls	Mental health conditions	Other neuro conditions	Mild TBI	Moderate-severe TBI	Healthy controls	Mental health conditions	Other neuro conditions
Negative affect	18–24	3.67 (0.57)	3.54 (0.22)	3.01 (0.68)	3.62 (0.65)	3.68 (0.78)	3.13 (0.65)	3.69 (0.20)	2.68 (0.53)	3.35 (0.66)	3.23 (0.64)
	25–45	3.62 (0.72)	3.90 (0.56)	2.70 (0.63)	3.39 (0.59)	3.36 (0.67)	3.13 (0.69)	3.04 (0.43)	2.61 (0.63)	3.31 (0.70)	3.26 (0.62)
	46–65	3.18 (0.70)	3.09 (0.63)	2.56 (0.60)	3.26 (0.67)	3.08 (0.71)	3.04 (0.77)	3.06 (0.98)	2.39 (0.56)	3.18 (0.77)	3.10 (0.65)
	>65	2.62 (0.65)	2.81 (0.16)	2.30 (0.55)	3.25 (0.74)	2.79 (0.54)	2.34 (0.34)	2.67 (0.51)	2.32 (0.51)	2.97 (0.55)	2.62 (0.49)
Fatigue	18–24	3.45 (0.79)	3.08 (0.12)	2.65 (0.70)	3.19 (0.83)	3.60 (0.76)	2.73 (0.68)	3.67 (0.76)	2.53 (0.66)	3.06 (0.71)	2.85 (0.69)
	25–45	3.56 (0.86)	3.93 (0.32)	2.52 (0.73)	3.39 (0.82)	3.32 (0.80)	2.94 (0.75)	2.92 (0.60)	2.40 (0.70)	3.00 (0.81)	2.99 (0.65)
	46–65	3.10 (0.99)	2.78 (0.73)	2.42 (0.75)	3.10 (0.73)	3.16 (0.83)	3.02 (0.92)	2.81 (0.79)	2.23 (0.68)	2.96 (0.90)	3.00 (0.80)
	>65	3.19 (0.64)	3.08 (0.83)	2.29 (0.68)	3.23 (0.69)	3.36 (0.93)	2.43 (0.62)	3.04 (0.34)	2.31 (0.63)	2.95 (0.59)	2.77 (0.50)
Executive function	18–24	2.28 (0.69)	3.36 (0.26)	2.18 (0.50)	2.40 (0.61)	2.73 (0.72)	2.49 (0.67)	2.67 (1.15)	2.20 (0.53)	2.42 (0.65)	2.42 (0.53)
	25–45	2.32 (0.75)	2.94 (0.67)	2.02 (0.53)	2.32 (0.57)	2.40 (0.52)	2.38 (0.68)	2.47 (0.66)	2.13 (0.55)	2.40 (0.57)	2.37 (0.57)
	46–65	2.13 (0.60)	2.04 (0.30)	1.96 (0.47)	2.17 (0.57)	2.22 (0.59)	2.21 (0.58)	2.36 (0.63)	2.00 (0.47)	2.27 (0.59)	2.43 (0.53)
	>65	1.82 (0.30)	1.68 (0.32)	1.81 (0.45)	2.31 (0.47)	2.04 (0.50)	2.24 (0.43)	2.07 (0.34)	1.92 (0.41)	2.20 (0.48)	2.08 (0.52)
Impulsivity	18–24	2.50 (0.70)	2.75 (0.35)	2.19 (0.66)	2.52 (0.60)	2.64 (0.65)	2.61 (0.75)	3.67 (0.72)	2.44 (0.75)	2.85 (0.76)	2.69 (0.67)
	25–45	2.39 (0.77)	2.79 (0.67)	1.99 (0.69)	2.25 (0.77)	2.34 (0.78)	2.56 (0.75)	2.55 (0.88)	2.24 (0.73)	2.63 (0.87)	2.66 (0.81)
	46–65	2.00 (0.71)	2.03 (0.34)	1.76 (0.56)	2.00 (0.59)	1.99 (0.60)	2.04 (0.69)	2.28 (1.00)	1.87 (0.59)	2.38 (0.81)	2.23 (0.59)
	>65	1.50 (0.35)	2.50 (0.35)	1.54 (0.41)	2.23 (0.75)	1.93 (0.40)	1.90 (0.58)	2.13 (0.72)	1.92 (0.52)	2.33 (0.76)	2.16 (0.63)
Substance abuse	18–24	1.81 (0.83)	2.50 (0.71)	1.16 (0.38)	1.58 (0.85)	1.61 (0.99)	1.73 (0.83)	2.78 (0.69)	1.41 (0.64)	1.88 (0.98)	1.73 (1.04)
	25–45	1.76 (0.96)	2.29 (1.45)	1.40 (0.63)	1.55 (0.73)	1.81 (0.93)	2.37 (1.10)	2.55 (1.27)	1.73 (0.81)	2.31 (1.11)	2.00 (1.00)
	46–65	1.39 (0.60)	1.67 (0.58)	1.28 (0.54)	1.48 (0.70)	1.31 (0.62)	1.81 (0.75)	1.96 (0.75)	1.40 (0.62)	2.01 (0.98)	1.64 (0.77)
	>65	1.14 (0.38)	1.67 (0.94)	1.07 (0.25)	2.00 (1.41)	1.33 (0.58)	1.53 (0.51)	1.08 (0.17)	1.24 (0.42)	1.39 (0.61)	1.15 (0.31)

BAST subscale	Education <or >HS	Women					Men				
		Mild TBI	Moderate-severe TBI	Healthy controls	Mental Health conditions	Other neuro conditions	Mild TBI	Moderate-severe TBI	Healthy controls	Mental health conditions	Other neuro conditions
Negative Affect	<HS	3.62 (0.59)	3.59 (0.86)	2.69 (0.65)	3.43 (0.62)	3.37 (0.73)	2.98 (0.70)	2.79 (0.22)	2.60 (0.60)	3.28 (0.66)	3.24 (0.68)
	>HS	3.38 (0.76)	3.30 (0.59)	2.56 (0.63)	3.36 (0.65)	3.24 (0.71)	3.08 (0.72)	3.09 (0.69)	2.50 (0.59)	3.24 (0.72)	3.14 (0.61)
Fatigue	< HS	3.53 (0.87)	3.42 (0.67)	2.50 (0.75)	3.29 (0.80)	3.37 (0.85)	2.70 (0.70)	2.83 (0.29)	2.44 (0.70)	2.90 (0.87)	2.92 (0.72)
	>HS	3.33 (0.90)	3.17 (0.81)	2.43 (0.73)	3.24 (0.80)	3.28 (0.79)	2.96 (0.81)	2.99 (0.70)	2.34 (0.68)	3.05 (0.74)	2.95 (0.63)
Executive Function	<HS	2.28 (0.64)	2.62 (0.62)	2.08 (0.54)	2.41 (0.54)	2.47 (0.60)	2.52 (0.64)	2.30 (0.76)	2.24 (0.56)	2.36 (0.61)	2.44 (0.49)
	>HS	2.21 (0.68)	2.38 (0.76)	1.92 (0.47)	2.22 (0.58)	2.31 (0.58)	2.29 (0.63)	2.41 (0.66)	2.02 (0.49)	2.35 (0.57)	2.32 (0.59)
Impulsivity	<HS	2.33 (0.80)	2.29 (0.33)	1.92 (0.67)	2.25 (0.71)	2.39 (0.72)	2.29 (0.81)	2.33 (0.95)	2.28 (0.77)	2.76 (0.80)	2.68 (0.80)
	>HS	2.21 (0.75)	2.46 (0.66)	1.79 (0.60)	2.21 (0.75)	2.17 (0.73)	2.39 (0.75)	2.55 (0.96)	2.09 (0.67)	2.50 (0.85)	2.52 (0.73)
Substance Abuse	<HS	1.52 (0.69)	1.78 (0.69)	1.32 (0.58)	1.62 (0.81)	1.64 (0.92)	2.20 (1.20)	2.89 (1.35)	1.58 (0.73)	2.14 (1.12)	1.80 (1.02)
	>HS	1.62 (0.85)	2.05 (1.11)	1.25 (0.52)	1.52 (0.77)	1.60 (0.84)	2.05 (0.93)	2.12 (1.07)	1.49 (0.70)	2.05 (1.02)	1.84 (0.95)

All values are mean (standard deviation) of the average score across items in each subscale.

Color values in the tables are to allow for comparison across tables of BAST subscales. Purple, negative affect; Green, fatigue; Blue, executive function; Red, impulsivity; Yellow, substance abuse.

TABLE 3 | Demographics and neurobehavioral symptoms in Spanish-speaking community-dwelling adults with and without TBI.

Participant characteristics		Spanish-speaking national cohort ($n = 350$)			
		Mild-severe TBI $n = 11$ **n (%)**	**Healthy controls** $n = 296$ **n (%)**	**Mental health conditions** $n = 27$ **n (%)**	**Other neuro conditions** $n = 16$ **n (%)**
Gender	Women	7 (63.6%)	112 (37.8%)	15 (55.6%)	5 (31.3%)
	Men	4 (36.4%)	182 (61.5%)	12 (44.4%)	11(68.8%)
	Transgender/Other	0 (0.0%)	2 (0.6%)	0 (0.0%)	0 (0.0%)
Race	White	7 (63.6%)	179 (60.4%)	15 (55.6%)	5 (31.3)%
	Black/African American	0 (0.0%)	10 (3.3%)	2 (7.4%)	3 (18.8%)
	Asian	0 (0.0%)	2 (0.7%)	0 (0.0%)	0 (0.0%)
	American Indian/ Alaskan Native	0 (0.0%)	2 (0.7%)	0 (0.0%)	2 (12.5%)
	Native Hawaiian/ Pacific Islander	0 (0.0%)	3 (1.0%)	0 (0.0%)	1 (6.3%)
	Other	3 (27.3%)	90 (30.4%)	10 (37.0%)	4 (25.0%)
	Unknown	1 (9.1%)	10 (3.4%)	0 (0.0%)	1 (6.3%)
Ethnicity	Hispanic	9 (81.8%)	280 (94.6%)	27 (100%)	14 (87.5%)
	Non-Hispanic	1 (9.1%)	10 (3.4%)	0 (0.0%)	1 (6.3%)
	Unknown	1 (9.1%)	6 (2.0%)	0 (0.0%)	1 (6.3%)
Education	≤High school	6 (54.5%)	144 (48.6%)	14 (51.9%)	8 (50.0%)
	>High school	5 (45.5%)	152 (51.4%)	13 (48.1%)	8 (50.0%)
		Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age (years)		37.8 (13.4)	38.8 (12.9)	39.1 (10.9)	35.3 (21.5)
Range		18–65	18–80	19–65	18–80
BAST subscales	Negative affect	3.40 (0.64)	2.51 (0.61)	3.21 (0.70)	3.19 (0.55)
	Fatigue	3.38 (1.01)	2.26 (0.72)	2.99 (0.86)	3.02 (0.86)
	Executive function	2.84 (0.84)	2.14 (0.56)	2.31 (0.63)	2.35 (0.50)
	Impulsivity	3.16 (0.68)	1.91 (0.71)	2.23 (0.70)	2.64 (0.93)
	Substance abuse	2.15 (1.08)	1.29 (0.60)	1.38 (0.57)	1.63 (1.15)

All BAST Subscale values are mean (standard deviation) of the average score across items in each subscale.
Color values in the tables are to allow for comparison across tables of BAST subscales. Purple, negative affect; Green, fatigue; Blue, executive function; Red, impulsivity; Yellow, substance abuse.

TABLE 4 | Neurobehavioral symptoms by gender and education among spanish-speakers.

BAST subscale	Women $n = 139$	Men $n = 209$	<HS $n = 172$	>HS $n = 178$
Negative affect	2.71 (0.67)	2.57 (0.33)	2.61 (0.67)	2.63 (0.67)
Fatigue	2.47 (0.84)	2.32 (0.78)	2.41 (0.80)	2.36 (0.82)
Executive function	2.14 (0.59)	2.21 (0.58)	2.31 (0.60)	2.06 (0.54)
Impulsivity	1.92 (0.70)	2.07 (0.80)	1.99 (0.80)	2.03 (0.74)
Substance abuse	1.20 (0.55)	1.43 (0.73)	1.31 (0.67)	1.36 (0.67)

All values are mean (standard deviation) of the average score across items in each subscale.
Transgender/Other not included in table due to low numbers when broken down by injury severity, age, or education.
Color values in the tables are to allow for comparison across tables of BAST subscales. Purple, negative affect; Green, fatigue; Blue, executive function; Red, impulsivity; Yellow, substance abuse.

frequent neurobehavioral symptoms than healthy controls and relatively comparable scores to those with TBI. Therefore, neurobehavioral symptoms common after TBI may be partially due to co-occurring neurological or mental health conditions and are not necessarily attributable to the injury itself.

Similar to past literature in both the general population (29, 31, 32), and after TBI (20, 21), we noted that women reported more fatigue symptoms and men reported more impulsivity and substance abuse symptoms across several health conditions. This suggests that gender affects neurobehavioral symptom reporting independent of the effects of TBI or other health conditions. The symptoms more commonly reported by women are also more common following a mild TBI (24, 48, 56). Given the higher proportion of women with mild vs. moderate-to severe TBI (both in our study and in the broader TBI population), it is difficult to tease out what is specific to injury severity vs. gender.

We did not note the same gender differences in our primarily Spanish speakers, other than men in the healthy control group reporting more substance abuse. This may be due to the small sample sizes, particularly in the TBI, Mental Health, and Other Neuro Conditions, as the descriptive data suggest a gender-based trend similar to those seen in those taking the survey in English. However, the sample size for Spanish-speaking healthy controls was robust, suggesting there may be a cultural component to symptom experience and/or reporting. Gender-associated differences in symptom reporting may be different for primarily Spanish speaking individuals (a proxy measure of level of acculturation) (57) living in the United States (58). The

TABLE 5 | Internal consistency reliabilities of the BAST subscales.

BAST subscale reliabilities	English-speaking (n = 2,511)				
	Mild TBI n = 211 α	Moderate-severe TBI n = 52 α	Healthy controls n = 1,548 α	Mental health conditions n = 427 α	Other neuro conditions n = 273 α
Negative affect	0.90	0.88	0.86	0.88	0.87
Fatigue	0.88	0.75	0.79	0.83	0.78
Executive function	0.88	0.86	0.80	0.81	0.80
Impulsivity	0.73	0.70	0.72	0.73	0.67
Substance abuse	0.77	0.81	0.70	0.76	0.80

BAST subscale reliabilities	Spanish-speaking (n = 350)			
	Mild-severe TBI n = 11 α	Healthy controls n = 296 α	Mental health conditions n = 27 α	Other neuro conditions n = 16 α
Negative affect	0.81	0.84	0.88	0.69
Fatigue	0.87	0.80	0.81	0.80
Executive function	0.90	0.78	0.83	0.69
Impulsivity	0.48	0.73	0.61	0.75
Substance abuse	0.91	0.73	0.71	0.93

Spanish-speaking group: TBI, MH, and Other Neuro all below minimum of n = 30 recommended to calculate reliabilities.
Color values in the tables are to allow for comparison across tables of BAST subscales. Purple, negative affect; Green, fatigue; Blue, executive function; Red, impulsivity; Yellow, substance abuse.

TABLE 6 | Neurobehavioral symptom differences between men and women by health condition in three cohorts.

Health conditions		BAST neurobehavioral subscales				
		Negative affect	Fatigue	Executive function	Impulsivity	Substance abuse
English national cohort	Healthy controls			$p < 0.001^a$	$p < 0.001^a$	$p < 0.001^a$
	Mental health conditions		$p = 0.001^a$		$p < 0.001^a$	$p < 0.001^a$
	Other neuro conditions		$p < 0.001^b$		$p = 0.001^a$	
	Mild-Severe TBI	$p < 0.001^b$	$p < 0.001^b$			$p = 0.001^a$
Spanish national cohort	Healthy controls					$p < 0.001^b$
	Mental health conditions					
	Other neuro conditions					
	Mild-severe TBI					

BAST, Behavioral assessment screening tool. Transgender/Other not included due to small cell sizes. M = Men; W = Women.
[a]M > W; [b]W > M; Alpha level for statistical significant set at α = 0.01.
Color values in the tables are to allow for comparison across tables of BAST subscales. Purple, negative affect; Green, fatigue; Blue, executive function; Red, impulsivity; Yellow, substance abuse.

cultural value placed on traditional gender roles, including the expectation that women are submissive and self-sacrificing and that men should be strong, virile, and indomitable in character (59), may contribute to under-reporting of fatigue symptoms in Spanish-speaking women and impulsivity and executive functioning symptoms in Spanish-speaking men living in the United States. The potential association between acculturation and symptom reporting is further supported in the comparisons based on survey language, wherein primarily Spanish-speakers reported less frequent fatigue, impulsivity, and substance abuse symptoms overall than native English-speakers.

The pattern of neurobehavioral symptom reporting by ethnicity group indicated that Hispanic individuals (including both primarily Spanish-speakers and English-speakers) experience more Negative Affect, Executive Function problems, and Impulsivity than non-Hispanic individuals. However, primarily Spanish-speakers reported *fewer* symptoms than native-English speakers did. This may reflect differences in level of acculturation; that is, primarily Spanish-speaking adults living in the United States are likely less acculturated than English-speaking Hispanic adults living in the United States (57). More acculturated individuals more often challenge traditional gender roles, reflecting the majority culture (60), whereas less acculturated individuals are more likely strongly influenced by traditional cultural values. In the absence of culture-based differences in symptom-reporting for more acculturated

TABLE 7 | Exploratory group comparisons of ethnicity and language by health condition in a national cohort of adults.

Health conditions		BAST neurobehavioral subscales					Ethnicity and language group differences
		Negative affect	Fatigue	Executive function	Impulsivity	Substance abuse	
Ethnicity	Healthy controls	$p < 0.001$		$p < 0.001$	$p < 0.001$		Hispanic > Non-hispanic
	Mental health conditions						
	Other neuro conditions						
	Mild-severe TBI			$p = 0.002$	$p < 0.001$		Hispanic > Non-hispanic
Language	Healthy controls		$p = 0.006$		$p = 0.003$	$p < 0.001$	E > SS
	Mental health conditions						
	Other neuro conditions						
	Mild-severe TBI				$p = 0.003$		SS > E

BAST, Behavioral Assessment Screening Tool. E = Native English Speakers; SE = Native Spanish Speakers reporting in English; SS, Native Spanish Speakers reporting in Spanish. $\alpha = 0.01$ for Kruskal-Wallace (p-values reported in cells) and $\alpha = 0.003$ for post-hoc Mann–Whitney U (Language comparisons).
Color values in the tables are to allow for comparison across tables of BAST subscales. Purple, negative affect; Green, fatigue; Blue, executive function; Red, impulsivity; Yellow, substance abuse.

Hispanic individuals, the negative impact of documented health disparities experienced by Hispanic individuals in the United States (43) may be more evident, as evidenced by the more frequent neurobehavioral symptoms they reported in the present study.

We anticipated that educational attainment would be associated with neurobehavioral symptoms, and we observed differences in Executive Function and Impulsivity, favoring those with some post-secondary education, in healthy controls. The direction of the association between these cognitive characteristics and educational attainment remains unclear. In the general population, lower Executive Function and more Impulsivity convey greater risk for lower educational attainment (61), but post-secondary education may also improve these cognitive functions (62). Despite past research suggesting educational attainment may be protective in the context of TBI, (63) we did not find any differences in neurobehavioral symptoms by education in the TBI or the other health condition groups. It may be that the cognitive consequences of TBI, other neurological conditions, and mental health conditions negate any protective effects of post-secondary education for higher-level cognitive functions. Further, research suggests that the protective effects of education for depression may be most evident in individuals from disadvantaged backgrounds (35, 36) which we did not account for in the educational group comparisons. Further study is warranted to explore how education may be a moderating factor contributing to neurobehavioral symptoms after TBI.

LIMITATIONS

Despite a robust sample size overall, the sample size was small for certain conditions within each cohort, especially when breaking the condition groups down further by gender and age or education. This is especially true for Spanish-speakers with TBI, making inference more difficult. Past literature, especially in TBI, has failed to adequately represent non-binary gender; though we did include Transgender/Other as a gender option, the sample size was too small to include in gender group comparisons or to provide a representative picture of these individuals. Finally, though multiple steps were taken to ensure validity of all collected data, data collected via anonymous survey are prone to bias and error.

CONCLUSIONS

Neurobehavioral symptoms are, indeed, more common in chronic TBI than in a neurologically healthy population. However, these symptoms are also partially attributable to personal factors, like age, gender, and ethnicity, and to health history, including other neurological conditions and mental health conditions. The interactions among cognitive, emotional, personality, biological, and environmental factors contribute to the complexity of neurobehavioral symptoms after TBI. The detailed characterization we present, in English- and Spanish-speaking healthy controls, adults with TBI, and adults with other neurological and mental health conditions from across the United States reveals unique patterns to aid in research on, and clinical interpretation of, neurobehavioral dysfunction after TBI.

DATA AVAILABILITY STATEMENT

The dataset generated for this study will not be made publicly available. The corresponding author can provide the dataset upon request and execution of the necessary data use agreements.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Texas Southwestern Medical Center Institutional Review Board. Written informed consent for participation was not required for this study in accordance with institutional requirements.

AUTHOR CONTRIBUTIONS

All authors have made significant contributions to the conceptualization, interpretation, and writing of this manuscript and the study described herein and have read and approved the final manuscript. SJ principal investigator on the study presented in this manuscript and was the primary author responsible for writing, conceptualization, and final decisions. AN contributed to data preparation, conducted extensive literature review, and drafted significant portions of the manuscript. LT collaborated with SJ in the initial study conceptualization, provided consultation on all statistical analysis as a statistician, and drafted significant portions of the methods and results.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01210/full#supplementary-material

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SYSTEMATIC REVIEW
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The Efficacy and Harms of Pharmacological Interventions for Aggression After Traumatic Brain Injury—Systematic Review

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Background: Aggression is a commonly reported problem following traumatic brain injury (TBI). It may present as verbal insults or outbursts, physical assaults, and/or property destruction. Aggressive behavior can fracture relationships and impede participation in treatment as well as a broad range of vocational and social activities, thereby reducing the individual's quality of life. Pharmacological intervention is frequently used to control aggression following TBI. The aim of this systematic review was to critically evaluate the evidence regarding efficacy of pharmacological interventions for aggression following TBI in adults.

Methods: We reviewed studies in English, available before December 2018. MEDLINE, PubMed, CINAHL, EMBASE, PsycINFO, and CENTRAL databases were searched, with additional searching of key journals, clinical trials registries, and international drug regulators. The primary outcomes of interest were reduction in the severity of aggression and occurrence of harms. The secondary outcomes of interest were changes in quality of life, participation, psychological health (e.g., depression, anxiety), and cognitive function. Evidence quality was assessed using the Cochrane Risk of Bias tool and the Joanna Briggs Institute Critical Appraisal Instruments.

Results: Ten studies were identified, including five randomized controlled trials (RCTs) and five case series. There were positive, albeit mixed, findings for the RCTs examining the use of amantadine in reducing irritability ($n = 2$) and aggression ($n = 2$). There were some positive findings favoring methylphenidate in reducing anger ($n = 1$). The evidence for propranolol was weak ($n = 1$). Individual analysis revealed differential drug response across individuals for both methylphenidate and propranolol. The less rigorous studies administered carbamazepine ($n = 2$), valproic acid ($n = 1$), quetiapine ($n = 1$), and sertraline ($n = 1$), and all reported reductions in aggression. However, given the lack of a control group, it is difficult to discern treatment effects from natural change over time.

Conclusions: This review concludes that a recommendation for use of amantadine to treat aggression and irritability in adults following TBI is appropriate. However, there is a need for further well-designed, adequately powered and controlled studies of pharmacological interventions for aggression following TBI.

Keywords: traumatic brain injury, TBI, aggression, irritability, pharmacotherapy, intervention, review

INTRODUCTION

Rationale

Problems with aggression, including agitated and irritable behavior, anger, verbal outbursts, physical assaults and property destruction (1–6), are common after traumatic brain injury (TBI) (7). Indeed, a recent review of epidemiological studies found an incidence of verbal and physical aggression post TBI across the spectrum of severity of 25–39% (8). The evolution and resolution of symptoms over time varies greatly (6), with aggression persisting for many decades after injury in some individuals (1–4, 9, 10). Aggressive behavior may limit access to rehabilitative treatment, participation in employment and in valued community activities (e.g., sports clubs, volunteering), as well as contribute to loss of friendships and romantic relationships (3, 4, 9, 11, 12). At the more severe end of the spectrum, aggressive behavior post TBI can result in violent crime, intimate partner violence, and ultimately incarceration (13–15).There may be unwanted changes in important family roles (3) due to strained marital relationships and difficulties with caring appropriately for children (3, 16). Family members have reported pervasive fear of aggressive outbursts, with concerns for their physical safety and potential legal consequences for the individual with TBI (5, 11, 17–19). Episodes of verbal and physical aggression can be traumatizing for families, leading to depression and anxiety in family members (3, 5, 11, 17–19). Aggression may also increase the burden of caring for the person with TBI, causing financial strain, change in relationships with other family members and result in lower quality of life (3–5, 17, 19).

The etiology of aggression following TBI is complex and multi-faceted (6, 20). Each occurrence of aggressive behavior is thought to be the product of varied interactions between damaged neural systems, cognitive impairments, and pre-morbid factors, which are exacerbated by post-injury and environmental factors. Within the relatively limited neurobiological research to date, damage to the frontal lobes, specifically the pre-frontal cortex, has been consistently associated with aggression post TBI (21–23). Pre-morbid factors may include personality traits, poor social functioning, pre-existing mental illness, and substance abuse (20, 22). Post-injury factors include medical and psychiatric comorbidities, poor emotional insight, medication, problems with sleep and fatigue, and environmental factors including interactions with family/carers, financial strain, and lack of control over everyday activities and being placed in overly demanding situations (3, 4, 6, 7, 9, 11, 20, 22, 24–27). With respect to comorbid psychiatric conditions, depression is thought to be strongly associated with aggression (7, 8, 12, 22, 28). In the acute stages of recovery from TBI when the patient is in post-traumatic amnesia (PTA), aggression appears to be largely underpinned by confusion, disorientation, and generalized cognitive impairments that resolve to a significant degree with emergence from this state. Aggression does not extend beyond PTA for many patients (29). Therefore, it is arguable that clinicians should differentiate between aggression occurring in the post-acute period, and agitation within the period of PTA. This review will therefore focus on post-acute management of aggression.

Numerous options for the management of aggressive behavior post TBI have been advocated in the literature, including both pharmacological and non-pharmacological approaches (30). Non-pharmacological treatment methods, including cognitive behavioral therapies, psychotherapy, relaxation-based therapies, skills-training programs, exposure-based treatments, behavioral interventions, and multicomponent treatments, have shown varying levels of success (31–33). Pharmacological methods are more commonly used. Given there are no FDA (Food and Drug Administration) approved medications for aggression post TBI, all medication is prescribed off-label (34, 35). As such, clinicians must rely on their clinical expertise, experience in treating similar conditions, extrapolation of aggression management from non-TBI populations, and consideration of other factors that may preclude certain medications such as availability and cost (34, 36). This has facilitated wide variation in prescribing practices, with anti-convulsants, anti-depressants, and anti-psychotics being the most commonly prescribed (35, 37).

Although this topic has attracted a number of previous reviews, many are outdated and their conclusions are limited by methodological issues, for example, lack of key systematic review components (no comprehensive search for published and unpublished data; lack of comprehensive evidence tables; no methodological assessment for risk of bias) (36, 38–43), failure to examine harms (40), and absence of a clear delineation between studies in which participants were in or out of PTA (34, 36, 44, 45). With respect to the findings from previous reviews, all have agreed that no strong conclusions could be drawn due to the limited number of studies and overall weakness of the evidence for each class of medication (34, 39, 41). Notwithstanding this, there was a general consensus that the current best evidence for treatment of aggression post TBI supports the use of amantadine and beta-blockers, with typical neuroleptics only to be prescribed with caution due to concern regarding adverse events (34, 36, 38, 41, 42, 44–47). Many other drugs have also been listed as possible options including anticonvulsants (mostly carbamazepine, valproic acid), specific serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCA), atypical antipsychotics, methylphenidate, and lithium (40–42, 44, 46, 47).

TABLE 1 | Deviations from protocol.

Original criteria	Change	Justification
Eligible participants must be adults aged 18 years and above	Participants were required to be adults aged 16 years and over, of either gender (studies where >80% of the sample was within this age range were also eligible)	The minimum age accepted for inclusion was reduced from 18 to 16 years old in order to be consistent with international definitions of the start of adulthood. The inclusion criteria was also broadened to state that 80% or more of the participants had to be in this age range. This catered for studies in which the inclusion criteria did not include an age range and/or when the sample age was only provided as mean and standard deviation with no range provided
Traumatic brain injury of any severity will be accepted for the review—as diagnosed using any recognized criteria	"Recognized criteria" (i.e., GCS, PTA, LoC, coma) were not required for inclusion	Inclusion criteria broadened due to paucity of studies. Review authors agreed that if the study authors deemed the patient to have had a TBI and/or were assessing them in a hospital/rehabilitation outpatient setting and/or the cause of the injury was clearly TBI (e.g., gunshot wound), this was sufficient
RCTs to be excluded	RCTs were eligible for inclusion in this review	The original intention was to separate this review into two reviews; focusing on RCTs and non-RCTs. However, due to the paucity of studies, it was decided to combine the study designs in a single review
Risk of bias will be assessed using the Newcastle-Ottawa Scale	Risk of bias was assessed using the Cochrane tools (RCTs) and the Joanna Briggs Institute tools (non-RCT)	The review team felt these tools provided a clearer assessment of methodological quality

GCS, Glasgow Coma Scale; LoC, loss of consciousness; PTA, post-traumatic amnesia; RCT, randomized controlled trial; TBI, traumatic brain injury.

Due to the lack of robust clinical research and strong recommendations from reviews, guidelines for the management of post-TBI aggression are largely absent. Two identified guidelines, which are now between 6 and 13 years old, provide some recommendations, albeit limited by the poor quality of the studies and reviews on which they were based (48, 49). Both guidelines advocated for beta-blockers (propranolol and pindolol) as a treatment option, with the earlier guideline from 2006 also listing methylphenidate, SSRIs, valproate, lithium, TCAs, and busiprone as alternative treatment options (48).

Objectives

In light of the paucity of evidence regarding management of aggression post TBI for patients who have cleared PTA, the present study aimed to systematically review the efficacy and harms of pharmacological therapies, as compared to all types of comparators, for aggression post TBI. This review also examined, as secondary outcomes, quality of life, participation, changes in psychological health (e.g., depression, anxiety, distress), and cognitive function. This review specifically addresses limitations in the extant literature by including a rigorous and comprehensive literature search, examination of harms, and methodological assessment for risk of bias. Further, only studies of post-PTA samples are included to ensure that the review focuses only on aggression after emergence from PTA. This provides clinicians with a thorough and detailed examination of all relevant evidence upon which to base prescribing decisions.

Research Question

The specific review question was: What are the efficacy and harms of pharmacotherapy as compared to all other comparators for the management of aggression in adults 16 years and over who have sustained a TBI?

METHODS

To ensure complete and transparent reporting, this review was conducted and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (50–52), and the reporting standards for literature searches and report inclusion criteria (53). The protocol for this review was published on the PROSPERO database (54). There were four deviations from the protocol, as described in **Table 1**.

Data Sources and Searches

In collaboration with an information specialist, we developed a comprehensive search strategy. Included were terms relating to the population (TBI) and intervention (pharmacotherapy). As this review forms part of a larger project reviewing evidence on a range of neurobehavioral symptoms (NBS) post TBI, aggression was not specified. The search strategy, undertaken on the title and abstract of records, used both keywords and controlled vocabulary with Boolean connectors. To source the keywords, the Cochrane Library and PubMed were searched: specifically, the titles, abstracts, and search strategies of relevant published systematic reviews.

All English language studies, regardless of publication status, available before December 2018, were eligible for inclusion (initial search undertaken in November 2016 and updated in May 2017, November 2017, and November 2018). The following databases were searched by the information specialist: MEDLINE [OVID SP interface (search strategy presented in **Appendix I**)]; PubMed (excluding MEDLINE); EMBASE (Excerpta Medica Database) (excluding MEDLINE, OVID SP interface); CENTRAL, and two discipline specific databases; PsycINFO (OVID SP interface); CINAHL (Cumulative Index to Nursing and Allied Health Literature).

Supplementary searching by author AH—who has received training in systematic review methodology and conducted previous searches—was undertaken in Research Gate and Google Scholar; international drug regulator websites (Food and Drug Administration, European Medicine Agency and the Medicines and Healthcare Products Regulatory Agency); clinical trial registries (the International Clinical Trials Registry Platform Search Portal and ClinicalTrials.gov; using search terms "traumatic brain injury" and "pharmacotherapy"); hand

searching titles in key journals [*Brain Injury* (1987 to March 2019), *Neuropsychology* (1987 to March 2019), *Journal of Neurotrauma* (1988 to March 2019), and *Journal of Head Trauma Rehabilitation* (1986 to March 2019)]; and by contacting academic and clinical experts chosen by the chief investigators ($n = 10$ contacted and responded). The reference lists, citations, and related articles were reviewed for all included studies and any relevant previous reviews of pharmacotherapy for TBI.

Inclusion Criteria

Studies were selected for this review on the basis of study design, participants, interventions, comparators, and outcomes.

Types of Studies

The following study types, regardless of sample size and study setting, were considered for inclusion: randomized controlled trials (RCTs), controlled non-randomized clinical trials, quasi-RCTs, controlled before and after studies, interrupted time series with a control group, interrupted time series without a parallel concurrent control group, analytical observational studies (including cohort and case–control studies), case series with pre-test/post-test outcomes, and single arm studies. All studies had to include a baseline measurement, and the aim of the study had to be the treatment of aggression.

Types of Participants

This review included participants who had sustained a TBI of any cause or severity, and presented with aggression after emergence from PTA. Participants were required to be adults aged 16 years and over, of either gender (studies where >80% of the sample was within this age range were also eligible). TBI had to be defined using recognized criteria such as brain imaging, loss of consciousness, Glasgow Coma Scale (GCS) score, or PTA. Where these were not provided, it was deemed sufficient that the study authors referred to the injury as "TBI" or "head trauma"; the patient was seen in a hospital/outpatient rehabilitation setting, and the cause of the injury was clearly TBI (e.g., gunshot wound to the head). Studies of acquired brain injury populations were only considered if the participants with TBI could be disaggregated. Although there were no restrictions on time since injury, participants had to be clear from PTA. If the sample appeared to contain both participants in PTA and out of PTA at baseline, studies were included if the data could be disaggregated or if >80% of the sample were not in the PTA period at any point during the study.

Aggression was conceptualized as either verbal or physical acts against property, others or self, and included descriptions of "agitation," "anger," and "irritability." Aggression that was sexual in nature was not included. Studies were accepted if they measured aggression using a validated assessment tool {e.g., Overt Aggression Scale-Modified for Neurorehabilitation (OAS-MNR) (55) or the Agitated Behavior Scale (ABS) (56)}. Medical/nursing notes or a log book were accepted if the results were presented quantitatively; qualitative descriptions of the behavior change were not deemed sufficient.

Types of Interventions

All pharmacotherapy interventions were eligible for inclusion in the review, with no restrictions on dose, duration, frequency, timing of delivery, or combination of drugs. Studies reporting mixed interventions (e.g., pharmacotherapy and psychological therapy) were considered for inclusion, provided the data for the pharmacotherapeutic intervention was reported separately.

Types of Comparators

All types of comparators were eligible for inclusion, including placebo, standard care, other non-pharmacological therapeutic intervention, and comparison of drugs within the same class. Studies of complementary medicines and over-the-counter medicines were included if they were used as a comparator or a co-intervention to a study drug.

Types of Outcomes

The primary outcomes of interest for this systematic review were changes in aggression (including changes in severity, frequency or type of aggression) and occurrence of harms. The secondary outcomes of interest were quality of life, participation, changes in psychological health (e.g., depression, anxiety, distress), and cognitive function. Studies were included if they reported on at least one primary outcome.

Study Selection

Throughout the study selection process, reviewers were not blinded to the journal titles, study authors, or their institutions. Titles and abstracts of all identified publications were screened by two independent reviewers for eligibility (AH and RB; FC and LP), and discrepancies were adjudicated by a third team member. Eligible citations were retrieved in full and assessed by pairs of independent team members (AH and RB; FC and LP), with disagreements resolved through discussion with a third reviewer.

Data Extraction and Assessment of Methodological Quality

For studies fulfilling inclusion criteria, three authors (AH, FC, and AJ) independently extracted data using a pre-piloted customized data extraction tool based on the standardized tool from the Joanna Briggs Institute System for the Unified Management, Assessment, and Review of Information (JBI-SUMARI) (57). The following data were abstracted: basic study identifying information (author names, publication year, country, financial support received), study methodology (design, sample, population, main inclusion and exclusion criteria, definition and measurement scales used for TBI and aggression, pharmacotherapy, comparator condition, co-intervention, outcomes, statistical analyses), study sample, and findings. All data extracted were checked and verified by the first author (AH). One author was contacted and provided clarification about study characteristics. Data were summarized using tables and narrative synthesis, with results grouped by the primary and secondary outcomes of interest. Study quality was independently assessed by three reviewers (AH, FC, and AJ)

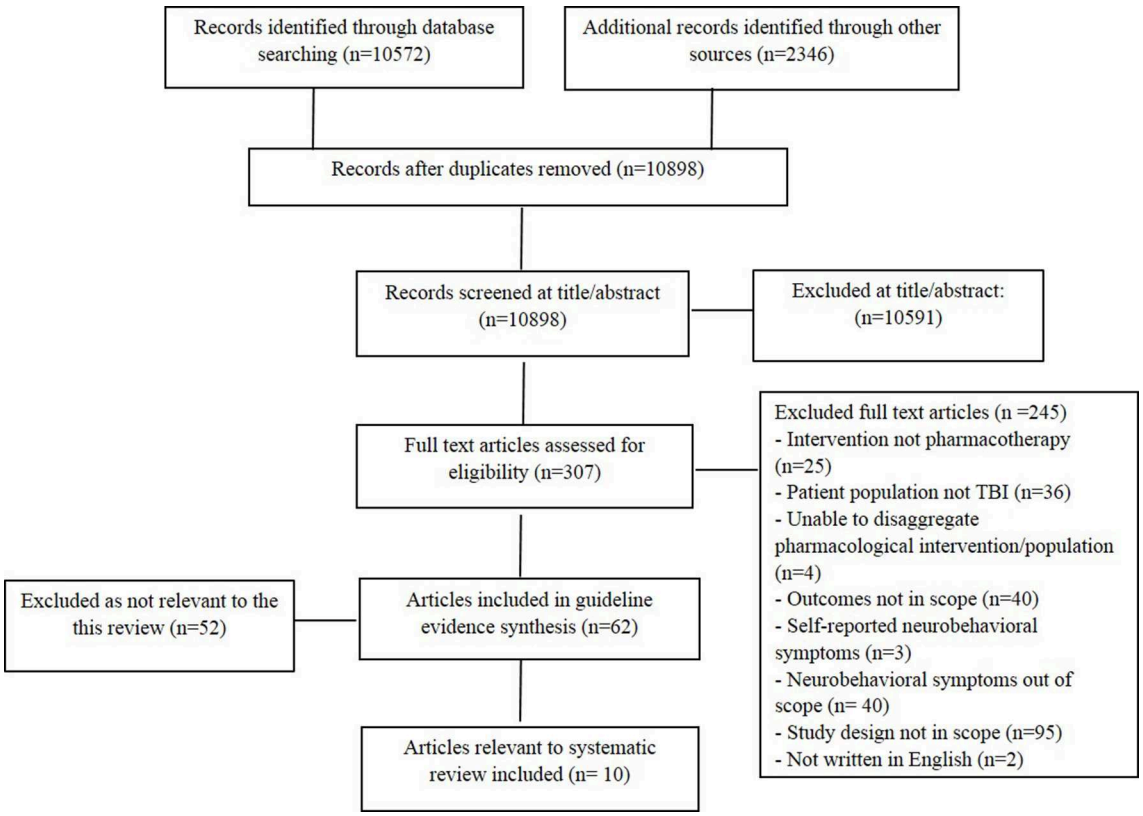

FIGURE 1 | Summary of studies excluded from narrative synthesis.

using the Joanna Briggs Institute critical appraisal instruments, with all decisions and supporting justifications reviewed and confirmed by author AH (57).

RESULTS

Study Selection

The literature search produced 12,918 articles, 10,572 from bibliographic databases and 2,346 from additional search sources. Title and abstract screening was completed on 10,898 articles, after 2020 duplicates were removed. Of the 307 articles reviewed at full text, 62 were deemed eligible for inclusion in the broader review (encompassing all NBS post TBI), with 10 studies eligible for the current review. **Figure 1** outlines the screening process and reasons for exclusion.

Study Characteristics

The 10 included studies were published between 1987 and 2017, and comprised 5 RCTs and 5 case series. The majority of studies were published in the USA, with one study from France. The sample sizes varied widely for the RCTs, ranging from 13 to 168, with the case series all having small sample sizes that ranged between 2 and 13 participants. Across the studies, there were more male participants; however, female participants were well-represented within many studies. The majority of participants were aged in their late 30s to early 40s. For those studies that reported on TBI severity, the full spectrum of severity, from mild to very severe, was captured. A variety of pharmacological interventions were examined, including anti-parkinsonian drugs ($n = 3$), anti-epileptics ($n = 3$), neurostimulants ($n = 1$), beta-blockers ($n = 1$), anti-depressants ($n = 1$), and anti-psychotics ($n = 1$).

Both primary outcomes for the review (i.e., changes in aggression and occurrence of harms) were addressed in each of the 10 studies, although, in one study, the findings with respect to harms were not provided (58). Of the secondary outcomes (i.e., quality of life, participation, changes in psychological health, and cognitive function), quality of life and participation were not addressed in any study and as such are not commented on further in this review.

Randomized Controlled Trials

The five RCTs examined the efficacy of methylphenidate (59), propranolol (60), and amantadine (61–63). Thirty-eight male patients with TBI were administered methylphenidate (up to 30 mg/day) or placebo in a single-blind RCT for 6 weeks. The outcomes examined were changes in aggression and anger measured on four validated assessment tools, the occurrence of harms, and changes in psychological health and cognition (59). A double-blind crossover design was used to examine

the effects of propranolol (initial dose of 60 mg and up to max 180 mg) on 13 patients more than 1 year post injury on agitation measured on the ABS and the occurrence of harms (60). Hammond et al. conducted all three studies examining the effects of amantadine using a parallel group, randomized, double-blind, placebo-controlled trial (61–63). The 2014 study (61) enrolled 76 patients, an average of 4–5 years post injury, who were administered either amantadine (100 mg; 2/day) or placebo for 28 days. Neuropsychiatric Inventory (NPI) subscales were used to examine irritability, agitation, and aggression. The occurrence of harms and impacts to psychological health was also measured. A large sample of 168 patients was included in the 2015 study (63), of whom 86 received placebo and 82 patients were administered amantadine (100 mg; 2/day) for 60 days. The irritability subscale of the NPI was used, along with a measure of harms and psychological health. The 2017 study (62) examined a subset of 118 individuals from the 2015 study (63) who had moderate to severe aggression, to examine the impact of amantadine on NPI agitation and aggression subscales, state and trait anger scores, as well as anger expression in this specific group.

Case Series

Five studies used an open label case series design to examine the effects of carbamazepine (64, 65), valproic acid (66), sertraline (58), and quetiapine (67) on aggression post TBI. Using a prospective open label trial, Azouvi et al. (64) examined the impact of carbamazepine (initial dose of 200 mg and up to max 800 mg) on agitation and anger outbursts in 10 patients over an 8 week period. The occurrence of harms and changes in cognitive function was also measured. The impact of carbamazepine was also examined in a second study, from which data on two patients with TBI could be extracted (65). The drug was administered over a 2 week period (increased from an initial dose of 200 mg 3/day until carbamazepine level could be obtained−8–12 μg/ml), with changes in assaultive behaviors and occurrence of harms documented. Similarly, the data for two TBI patients were extracted from a study by Wroblewski et al. (66) that also examined another anti-convulsant medication, valproic acid. Patient 1 was approximately 5 years post his injury and was administered 750 mg of valproic acid per day for 3 months. Patient 2 was 2.5 years post injury and was administered an initial dose of 500 mg per day of valproic acid, which was subsequently titrated up to a maximum dose of 1,500 mg per day over the 6 week data collection period. The impact of these interventions was documented by counts of acts of physical aggression and "time outs" for verbal aggression, as well as the occurrence of harms. Sertraline was administered to a group of 13 mostly male patients over an 8 week period. The initial dose was 50 mg per day, and this was titrated to 200 mg per day or the maximum tolerable dose. Irritability and aggression scales of the outpatient Overt Aggression Scale (OAS) were used, along with examination of harms and psychological health. Seven patients an average 1 year post injury were administered quetiapine over a 6 week period (initial dose 50–100 mg per day; maximum dose ranged from 25 to 300 mg) to examine the effects on the OAS, aggression subscale of the Neurobehavioral Functioning Inventory and clinician impression of change. Harms and impact on cognition were also assessed.

Synthesized Findings

Changes in Aggression/Anger/Irritability/Agitation

RCTs

Overall, the findings for the efficacy of methylphenidate, propranolol, and amantadine for treating post-TBI aggression were mixed, with analysis suggesting differential response patterns across individuals (59–63).

The efficacy of methylphenidate was assessed across four separate outcome measures, as well as an overall combined analysis across measures using hierarchical clustering (59). Methylphenidate was associated with a significant reduction in scores for trait anger, state anger, hostility, and belligerence (59). Hierarchical clustering produced two clusters within the treatment group; the "non-responders" (no reduction in anger scores from baseline to 6 weeks) and the "response group" (all members exhibited clear reduction in anger from baseline to 6 weeks). Discriminant analysis revealed that participants with higher baseline anger scores were more likely to respond to the drug than participants with low baseline anger scores (59).

The findings for efficacy of propranolol were mixed. Across the 10 patients, the magnitude of change in behavior measured by the ABS from baseline to intervention phase was 0.135, which denotes a "small or negligible" change. Individual analysis revealed three groups of response type; little or no effect ($n = 6$), moderate to strong effect—improvement ($n = 2$), and moderate to strong effect—worsening ($n = 2$).

The three studies of amantadine examined irritability, aggression, and anger (61–63). The findings with respect to irritability differed between studies. In the 2014 study, there was a greater reduction in overall irritability, as well as in the frequency and severity of the most problematic irritable behavior, over the 28 day intervention in the treatment group from the perspective of the observer (61). However, there was no significant change in the distress associated with the behavior (61). In comparison, the 2015 study examining amantadine use over a 60 day period found no significant differences between the groups (either at 28 or at 60 day follow-up) for the most problematic irritability behavior, most aberrant behavior, or the distress associated with the irritable behavior (from either the perspective of the participant or the observer) (63).

With respect to change scores for aggressive behaviors and associated distress, there was no significant difference in the change scores for the treatment and placebo groups from the perspective of an informant (61, 62). However, when the sample was restricted to only those who had scored >2 on the NPI-A, a significant difference in change scores was noted (61). Further, when participant ratings were collected in the 2017 study, there was statistically significant difference between the groups regarding the change in aggression scores and distress related to the behavior for Day 60, although not Day 28 (62). The 2017 study also examined state and trait anger as well as anger expression, finding no significant differences in group change scores (62).

Case series

The cases series provided mostly positive findings. Both the case series examining the effects of carbamazepine reported positive findings overall, with a reduction in the number of assaultive behaviors (65) and a significant improvement in irritability and disinhibition on the NRS-R and the ABS (64). Conversely, there was no significant change in hyperactivity–agitation, mood lability, excitation, or hostility on the NRS-R (64). There was also inter-individual variability in treatment response on the NRS-R; five patients showed a decrease over the intervention of 50% or more, three patients' scores decreased between 25 and 43%, and two patients showed no change (64). The two patients administered valproic acid showed improvements in verbal abuse, yelling, threats of assault, and physical aggression (66). Significant improvements were reported for both aggression and irritability for patients treated with sertraline, with 80% and 100% of patients demonstrating a clinically meaningful improvement at 8 weeks for aggression and irritability, respectively (58). For those administered quetiapine, there was a significant reduction in aggression documented on both the aggression subscale of the NFI and the OAS-M, and an improvement on the Clinical Global Impression scale (67).

Harms

Only one study did not report on the occurrence of harms (although it did state that clinical assessment for harms took place at each follow-up visit) (58). No adverse events were reported for valproic acid (66) or methylphenidate (59). Adverse events were reported for administration of carbamazepine (64), quetiapine (67), and propranolol (60). With respect to amantadine, there were no significant group differences in proportion or severity of adverse events (61–63); however, one participant required drug termination secondary to a seizure (61). Carbamazepine was associated with drowsiness ($n = 4$), requiring lowering of dosage, and a single serious adverse event was recorded, in which a patient experienced a significant allergic cutaneous reaction toward the end of the intervention period (day 51 of 56), requiring withdrawal of medication (64). Transient diplopia and ataxia, clearing spontaneously within 1 h were also reported (65); however, it was unclear if this occurred in the two TBI patients included in the current review. Quetiapine was associated with mild extrapyramidal side effects and akathisia in one patient, and three patients reported sedation that resolved by weeks 3 to 6 (67). Propranolol administration resulted in a paradoxical increase in agitation for two patients (60).

Cognition

There was no impact on cognitive functioning reported for carbamazepine (64) or methylphenidate (59). In contrast, there was a significant improvement in cognitive functioning on the RBANS (Repeatable Battery for the Assessment of Neuropsychological Status) for those administered quetiapine (67).

Psychological Health

Four studies addressed the impact of the intervention on psychological health. The administration of sertraline was associated with an improvement in depression scores at the 4 week follow-up, but not at the 8 week follow-up (58). There was no impact of sertraline on suicidality at either follow-up (58). There was an overall improvement in general psychopathology for those administered methylphenidate, as well as significantly greater reductions in the presence and severity of brain-injury related personality changes, as rated by both the patient and an informant (59). Amantadine was not associated with changes in scores on global mental health, depression, or anxiety symptoms, as rated by the participant or observer (61, 63). Conversely, the clinician rated Clinical Global Impressions–Global Improvement subscale did show greater global improvement for the treatment group at 60 day follow-up, but not at the earlier 28 day follow-up (63).

Other

Overall behavior was also noted to improve with carbamazepine, as was social functioning (64).

Risk of Bias

The five RCTs were assessed as having low to moderate risk of bias. Most commonly, studies did not clearly report how the random sequence was generated, how allocation concealment was maintained, or what were the procedures for blinding of participants, personnel, and outcome assessors. The case series were judged to have moderate to high risk of bias, and were inherently limited by lack of a control group. The areas of methodological weakness varied across studies and are outlined in **Supplementary Materials**. Across studies, there was some detail provided regarding co-interventions (e.g., drug class and a statement that dosage was stable during intervention). Three studies provided no information regarding co-interventions (58–60).

DISCUSSION

Summary of Main Findings

The primary aim of this systematic review was to evaluate the evidence for efficacy and harms of pharmacological interventions for aggression following TBI. Ten studies met inclusion criteria: five RCTs and five case series. Multiple studies examined the effects of anti-parkinsonian and anti-epileptic medications, with the remaining studies using neurostimulants, beta-blockers, anti-depressants, and anti-psychotics. Overall, this review concludes based on the evidence from three RCTs conducted in an outpatient community-based setting that there is sufficient evidence to make a recommendation for the use of amantadine in treating aggression and irritability after TBI in the post-PTA period.

The primary outcome, change in aggressive behavior, was measured in all studies included in the review. Three RCTs examined the impact of amantadine on irritability, aggression, and anger (61–63). It is postulated that amantadine may improve irritability and aggression through enhancing cognitive function and, through this mechanism, may enhance cognitive appraisal and behavioral disinhibition (61, 68). Overall, there was some positive, albeit mixed, findings for an effect of amantadine on

irritability and aggression in community-based samples (61–63), with no evidence found for reducing anger (62). The impact of amantadine on irritability was examined in two studies (61, 63). Both studies used a 28-day follow-up time point, with a further 60 day follow-up also included in the 2015 study. At the 28 day follow-up, only one of the two studies found a significantly greater reduction in irritability in the treatment group (61). However, when the results from these studies were combined in a meta-analysis, the pooled result did favor amantadine over placebo (63). At the 60 day follow-up, included in the 2015 study, there was no significant impact of amantadine on irritability (63).

The impact of amantadine on aggressive behavior was measured in two RCTs (61, 62). There was some evidence in favor of amantadine in treating aggression; however, outcomes varied for different follow-up time points, respondent types (i.e., participants vs. informants), and baseline aggression levels across the samples. For example, in the 2014 study, there were no significant differences found in the change scores for the treatment and placebo groups at 28 day follow-up (61). However, when the sample was restricted to only those with more severe aggression (score of >2 on NPI-A), a significant difference in change scores was noted. Although this suggests that amantadine may be more effective for those with more severe aggression, the finding is difficult to interpret in light of the non-significant findings at the 28 day follow-up in the 2017 study that restricted their sample to those with even greater aggression (inclusion criteria of 6 or more on NPI-A). With respect to the possible influence of time point and respondent type, significant results were found in the 2017 study for only the 60 day follow-up, and only from the perspective of the participant. The results for the 28 day follow-up were non-significant for both respondents and non-significant for the informants at the 60 day follow-up. Taken together, these results suggest that participants themselves with more severe aggression may notice an impact of amantadine on aggression over longer time periods.

The mixed evidence reported for amantadine in the Hammond studies may have been contributed to, in part, by a large placebo effect masking detection of a treatment effect (63). Indeed, findings from the control groups showed a reduction in aggression and irritability over the treatment period on a number of the measures administered (61–63). The placebo effect may have resulted from numerous factors including therapeutic alliance, the effect of behavior monitoring, inconsistency in baseline behavior month to month, participant expectations, and other non-specific effects (63). Although the research staff did not interact with patients in an explicitly psychotherapeutic manner, a type of therapeutic alliance may still have formed through kind and supportive interactions (63). It is suggested that larger sample sizes are required to power studies to find treatment effects in the context of robust placebo effects. Finally, the contrasting results from Hammond et al. (61–63) highlight the importance of including the perspectives of the participant, informant, and clinician, and ensuring that the intervention period and time points for follow-ups are of a sufficient duration to allow people to notice a change in behavior (63).

The remaining two RCTs examining the effects of propranolol and methylphenidate demonstrated mixed findings, with further analysis revealing inter-individual differences in response to these medications (59, 60). Specifically, the response to both propranolol and methylphenidate varied across study participants, with some responding favorably to the medication and others not showing any improvement in behavior (59, 60). Further, for 2 of the 10 patients administered propranolol, there was a worsening of behavior (60). Mooney and Haas (59) further analyzed those participants who responded favorably to methylphenidate, identifying that this group had, on average, higher baseline anger scores. Although this may suggest the simple effect of regression to the mean, the authors conducted the same analysis in the control group and found that those with higher anger scores at baseline did not show significantly greater change over time compared to those with lower anger scores at baseline. This suggests that a methylphenidate intervention may be more appropriate for those with more severe aggressive behaviors post TBI, and may be less efficacious for those with milder difficulties.

The case series provided positive findings for use of valproic acid (66), sertraline (58), and quetiapine (67). Of the two studies examining carbamazepine, one reported uniformly positive findings (65), with mixed findings reported by Azouvi et al. (64), who found inter-individual variability in treatment response. Although these findings provide some support for the use of each of these drugs in specific individuals, lack of a control group limits the conclusions that can be drawn, as the studies cannot account for natural recovery over time. Of note, of the two patients administered valproic acid, a drop in serum concentration coincided with a flare in behavior, which resolved with increasing the valproic acid dose (66). This suggests that the change in behavior may have been, at least in part, influenced by administration of valproic acid.

Of the nine studies that reported on harms, no adverse events were reported for valproic acid (66) or methylphenidate (59). Adverse events were reported for carbamazepine (64), quetiapine (67), propranolol (60), and in one of the amantadine studies (61). Carbamazepine was associated with drowsiness, a single significant allergic cutaneous reaction requiring withdrawal of medication (64), and transient diplopia and ataxia (65) (it was unclear whether this occurred in the two TBI patients included in the current review). Quetiapine was associated with mild extrapyramidal side effects and akathisia in one patient, and three patients reported sedation that resolved (67). Propranolol administration resulted in a paradoxical increase in agitation for two patients (60). Although adverse events were mostly non-serious and, in some cases, transient, the impact of harms must be considered in the context of TBI, that is, how much the undesired effect weighs on the neurological recovery of a patient who may also have a cognitive and motor deficit, and the impact of such effects on the patient's ability to engage with other rehabilitation services (69). For example, drowsiness, which may be considered a minor and manageable issue in non-TBI populations, may significantly impact an individual with TBI who is already challenged by significant fatigue and is attempting to engage in demanding cognitive and physical tasks such as physiotherapy. Finally, to increase transparency and consistency among trials, the use of standard reporting of adverse events, for

example, using terminology from MEdDRA (Medical Dictionary for Regulatory Activities), is recommended.

Only two of the four secondary outcomes were reported on across the RCTs and case series: cognitive function and psychological health. Only quetiapine was associated with a positive change in cognition (67), with the other two studies reporting on this outcome failing to find a significant impact of carbamazepine (64) or methylphenidate (59). Notably, Hammond et al. (70) recently published a study examining the impact of amantadine on cognitive functioning in a sub-group of individuals ($n = 119$; participants were eligible if their performance on two or more neuropsychological measures fell below one standard deviation from normative means of the overall sample) from the 2015 study (63). This study found that cognitive function was not improved by amantadine (70). Psychological health, overall behavior, and social functioning improved for those administered methylphenidate (59) and carbamazepine (64). This raises the possibility that the therapeutic benefit of these drugs may not be specific to anger but rather reflect an overall lowering of psychopathology. In contrast, sertraline administration produced some limited and transient positive effects on depression, and was not associated with changes in suicidality (58). The authors concluded from this that the gains noted in aggressive behaviors and irritability could not be explained as the secondary effects of successfully treating a mood disorder (58). Collectively, these studies raise an important issue about the mechanism of action for these drugs in TBI populations, and the importance of considering comorbid factors, such as mood disorders, in prescribing practices. Finally, the impact of amantadine on global mental health was only identified by clinicians, not the participant or informant (61, 63), suggesting that clinicians were able to perceive more subtle changes in behavior and mood, which may have become apparent to participants and informants over longer follow-up periods.

Risk of Bias

The RCTs were assessed as having low to moderate risk of bias. Most commonly, studies did not clearly report exactly how the random sequence was generated, how allocation concealment was maintained and the procedures for blinding of participants, personnel, and outcome assessors. The case series were judged to have moderate to high risk of bias and are inherently limited by lack of a control group. Across most studies, there was some limited detail provided regarding co-interventions (e.g., only providing drug class and a statement that dosage was stable during intervention), with three studies failing to provide any information regarding co-interventions (58–60). Further details about co-interventions should be provided in future studies to allow readers to determine possible synergistic or, conversely, antagonistic effects of any co-intervention. Finally, one study was supported by an "unrestricted educational grant from Pfizer, Inc." (58).

Summary and Implications of Review

Overall, the evidence in favor of amantadine suggests that a trial of amantadine in patients with aggression or irritability after TBI (and post PTA) may be of benefit, and should be considered in the outpatient setting. The RCT evidence for methylphenidate and propranolol was deemed insufficient to draw conclusions, and as such no recommendations are made for these medications. Likewise, the evidence from the case series examining use of carbamazepine, valproic acid, sertraline, and quetiapine is considerably limited by the study design and risk of bias, with further evidence required to formulate strong conclusions for these medications.

This review highlighted how an individual's response to medication may vary widely from the overall analysis. This is not surprising given the myriad factors that can lead to post-TBI aggression, and which may, along with other factors, impact medication metabolism and efficacy. It is possible that some of the factors influencing aggression are yet to be identified (60), and it suggested that further work should be done to identify such factors. This finding also raises the question as to whether the end point of "statistically significant" group level change is the best way to evaluate these trials. It may instead be more helpful to review the proportion of participants with "clinically meaningful" change on the primary outcome measure in the treatment and control groups, as was done by Hammond et al. (61–63).

With respect to trial design, one suggestion would be a design wherein RCTs are still used; however, when a patient fails to respond to a particular drug, they are moved (following a wash out period) to a new intervention arm with a different pharmacological intervention. The characteristics of the participants in each treatment responsive group could then be analyzed in an attempt to identify factors that suggest a person will respond to a particular drug (i.e., TBI-related factors such as area and extent of damage, presence of co-interventions, history of significant substance abuse). It is acknowledged, however, that such multi-step trials are difficult to obtain funding for and challenging to implement. Translated into clinical practice, a framework could be provided with factors or combinations of factors that should be considered when prescribing medications for post-TBI aggression, and how these might increase or decrease the likely efficacy of specific medications. This idea is consistent with growing support within the literature of a need for an individualized approach to medication in TBI patients (34, 38, 44, 45, 69). The concept of considering a range of pertinent factors in drug choice is hardly novel. However, a comprehensive evidence base to guide such decision making within the TBI population is lacking.

Limitations

This review was limited by lack of an assessment for publication bias. However, the search strategy included a comprehensive search for unpublished studies through clinical trial registries, food and drug regulators, and correspondence with key authors. It is notable that a number of studies were excluded at full text because they failed to clearly differentiate whether patients were in the PTA period. This is important as there may be significant differences in the factors that lead to the development and maintenance of aggression in and out of

PTA. For our understanding of aggression post TBI and its management to progress, study samples should be restricted to patients who are clearly in or out of PTA. Notwithstanding the noted limitations, this review represents an important systematic analysis of the evidence for pharmacotherapy for aggression post TBI that has included both efficacy and harms and used a comprehensive search strategy and analysis of methodological quality.

CONCLUSIONS

Aggression is a potentially debilitating condition that can occur following TBI and reduce quality of life. This review concludes that a recommendation for use of amantadine to treat irritability and aggression in adults following TBI is appropriate. However, further research is needed to strengthen the evidence base, with larger sample sizes and consistent methodology across studies to allow for meta-analysis of findings. A pattern of inter-individual differences in treatment response was prominent in many studies, highlighting the possible use of "clinically meaningful change" as an alternate outcome measure, and use of trials with multiple intervention arms with participants being swapped between arms following treatment failures. Understanding the factors or constellation of factors that impact upon treatment success is a key issue to be examined in future studies, with long follow-up time points and data collection from multiple sources also recommended.

AUTHOR CONTRIBUTIONS

The searches, study selection, data extraction, and risk of bias were conducted by AH, FC, AJ, LP, and RB, with supervision provided by JP. AH completed the data synthesis with assistance and supervision provided by AJ and JP, respectively. AH led the drafting of the manuscript. All authors contributed to editing and reviewing of the manuscript and conception and design of this review.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01169/full#supplementary-material

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Conflict of Interest: One of the chief investigators MH has given talks on this topic for which travel and accommodation has been paid by the organizers. In addition, he has accepted fees for consulting and research from the pharmaceutical companies—Bionomics, Eli Lilly, Janssen-Cilag, Lundbeck, Novartis, Pfizer, Praxis, Servier, and Lundbeck.

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BRIEF RESEARCH REPORT
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Cohort Differences in Neurobehavioral Symptoms in Chronic Mild to Severe Traumatic Brain Injury

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Our understanding of neurobehavioral symptoms after traumatic brain injury (TBI) largely relies on data gathered in studies conducted at academic medical centers or large clinical centers with research infrastructure. Though this often provides a well-characterized clinical sample, it may also introduce bias based on geographic locations served by these institutions and personal factors associated with patient access to these institutions. We collected neurobehavioral symptoms via the self-reported Behavioral Assessment Screening Tool (BAST) in a National TBI Cohort ($n = 263$) and a Medical Center TBI Cohort ($n = 218$) of English-speaking community-dwelling adults with chronic TBI. The primary focus of the present study was to compare demographics and neurobehavioral symptom reporting across the two cohorts and to discuss the implications of any such differences on interpretation of symptom scores. Across all BAST subscales (Negative Affect, Fatigue, Executive Function, Impulsivity, and Substance Abuse), participants in the National TBI Cohort reported significantly more frequent symptoms than those in the Medical Center TBI Cohort (p's < 0.001). Participants in the National TBI Cohort were more likely to be non-White and Hispanic compared to the Medical Center TBI Cohort, and those with mild TBI in the National TBI Cohort were more likely to have less than a high school education than those with mild TBI in the Medical Center TBI Cohort. Individuals with TBI recruited through academic and clinical institutions may not be representative of individuals with TBI living across the United States.

Keywords: traumatic brain injury, behavior, emotion, education, health disparities

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INTRODUCTION

Neurobehavioral symptoms, including aggression, disinhibition, lack of motivation, and difficulty planning/executing actions (1, 2), are common after traumatic brain injury (TBI) and adversely affect participation and quality of life even many years after injury (3–9). Race and/or ethnicity (10), education (11), and gender (12, 13) may also contribute to differences in neurobehavioral symptoms after TBI. Racial and ethnic minority groups report more psychiatric symptoms and cognitive deficits after TBI than non-Hispanic white individuals (10, 14–16). Racial and ethnic minorities also experience healthcare disparities after brain injury (14, 16–22) that can magnify the long-term consequences of injury (14, 23–25). A review by Arango-Lasprilla and Kreutzer (14) on the effects of racial and ethnic disparities on functional, psychosocial,

and neurobehavioral outcomes after TBI concluded that, compared to non-Hispanic white individuals, individuals from racial and ethnic minority groups received lower-quality treatment and had worse functional outcomes. The authors suggest multiple potential mediating factors between race/ethnicity and poor outcomes, including socioeconomic status, quality (not just quantity) of education, access to care, quality of care, and transportation barriers (14). These factors are also all associated with where an individual lives. In the general population, geographic location (e.g., proximity to high quality medical care) is associated with symptoms, long-term outcomes, and health service utilization (26, 27). For individuals with TBI, those living in more rural areas, as compared to those living in more urban areas, have more pre- and post-injury comorbities and report more unmet service needs (28). Unmet needs may be the result of fewer rehabilitation professionals, services, and facilities available in rural areas (29).

Our understanding of neurobehavioral symptoms after TBI largely relies on data gathered in studies conducted at academic medical centers or large clinical centers with research infrastructure. Though this often provides a well-characterized clinical sample, it may also introduce bias based on geographic locations served by these institutions. Geographic location affects patient access to these institutions and is likely a proxy indicator of other factors related to healthcare disparities noted above. To determine whether neurobehavioral symptoms after TBI are associated with geographic location and different recruitment strategies, this study compared neurobehavioral symptoms from a nationally representative sample of adults with chronic TBI assessed anonymously to a sample of adults with chronic TBI recruited from multiple academic medical and clinical centers.

MATERIALS AND METHODS

Setting

We collected neurobehavioral symptoms via a validated self-reported survey in two study cohorts of community-dwelling adults with chronic TBI. The first (National TBI Cohort) was a nationwide self-reported survey of community-dwelling adults with self-reported TBI collected electronically via Qualtrics™. The second (Medical Center TBI Cohort) was a combined data set of three separate studies including community-dwelling adults with a chronic history of documented TBI recruited through academic medical centers in major metropolitan areas and their surrounding communities. Study 1 was the first to pilot the BAST in community-dwelling adults with TBI (30). Study 2 was a randomized clinical trial of a healthy lifestyle weight loss intervention vs. education intervention for community-dwelling adults with TBI that collected the BAST during the baseline assessment (31). Study 3 piloted the BAST as part of the Concussion Network of North Texas (ConTex) research registry on concussion recovery.

Participants

National TBI Cohort

Participants were adults (≥18 years old), fluent in English, with a self-reported history of TBI and no self-reported history of schizophrenia or dementia, who electronically consented to participate in this anonymous survey study.

Medical Center TBI Cohort

All participants were community-dwelling adults (≥18 years old), fluent in English, with a documented history of TBI. Specific inclusion/exclusion criteria for each of the three studies are as follows:

Study 1 participants were ≥18 years old and at least 3 months post moderate–severe TBI. Inclusion criteria were as follows: (1) documented complicated mild to severe TBI, (2) ≥3 months post-injury, (3) >18 years old, and (4) written English fluency. Exclusion criterion was inability to provide informed self-consent. We collected age, gender, race, education, time since injury, and the BAST via paper questionnaires mailed to study participants.

Study 2 participants were 18–64 years old and at least 6 months post moderate–severe TBI. Inclusion criteria were as follows: (1) 18–65 years old, (2)≥6 months post-injury, (3) moderate to severe TBI, (4) BMI ≥ 25 kg/m^2, and (5) access to or willingness to use a smartphone. Exclusion criteria were as follows: (1) contraindicated health conditions, (2) non-English fluency, (3) non-community dwelling, and (4) taking diabetes medication.

Study 3 participants were those >20 years old who attended an initial clinic visit at an academic medical center clinic for a mild TBI (e.g., concussion). Inclusion criteria were as follows: (1) diagnosis of concussion presenting at a participating clinic, (2) visual acuity/hearing adequate to complete interviews and questionnaires, (3) English fluency, and (4) ability to provide informed consent. Exclusion criteria were as follows: (1) loss of consciousness >30 min, (2) known skull fracture or intracranial bleed, (3) spinal cord injury with SIA score of C or worse, and (4) most recent concussion occurring >6 months ago.

Procedures

National TBI Cohort

We collected all data using Qualtrics™ (Qualtrics, Provo, UT) online, HIPAA-compliant survey platform. We previously provided a detailed description of the data collection for this cohort and the methods to ensure integrity of the data collected (32). Briefly, we leveraged Qualtrics not only for the online platform but also for its capacity to serve as a survey panel aggregator to collect survey responses from a national sample. We confirmed TBI presence and severity with an electronic version of the OSU-TBI (33); prior studies indicate that collecting OSU-TBI data via electronic survey is valid (34). We generated a map of all responses to show national representation, depicted in **Figure 1**.

Medical Center TBI Cohort

Study 1: Adult participants with TBI were recruited through two academic medical centers' rehabilitation research registries and previous and ongoing research studies. We collected the demographic data and BAST, in addition to a number of other measures, via paper questionnaires. Documentation of TBI was

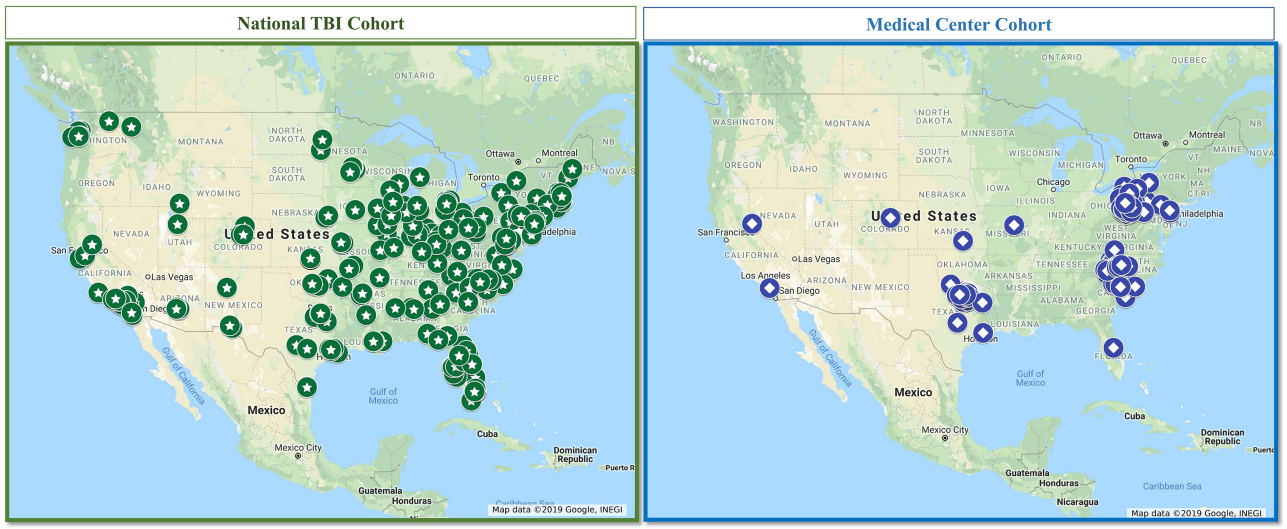

FIGURE 1 | Map of participants from the National TBI Cohort and the Medical Center Cohort.

available through medical record review and/or participation in previous research studies.

Study 2: Adult participants with TBI were recruited through an academic medical center, a major healthcare system, and the community in a large, metropolitan area. We collected demographic data (age, gender, race, ethnicity, and education) at baseline via interview and the BAST at baseline via electronic survey in RedCap™.

Study 3: ConTex recruits individuals age 5 and over from local concussion clinics in the North Texas area; for the purposes of this study, we included only adults >20 years old, as an adolescent version of the BAST is collected in ConTex for individuals 12–20 years old. We collected the BAST as part of the 3 month post-initial clinic visit follow-up assessment completed electronically via REDCap™.

Full Medical Center TBI Cohort: We generated a map of all participants in the Medical Center TBI Cohort, depicted in **Figure 1**, to show geographic representation compared to the National TBI Cohort.

All studies were approved and overseen by their respective institution's Institutional Review Board prior to any study procedures.

Measures

National TBI Cohort

A demographic questionnaire captured age, gender, race, ethnicity, and highest level of education completed. This study included only individuals indicating a history of TBI or concussion on a checklist of various health conditions. These participants also completed a questionnaire following the structure and content of the OSU-TBI, to confirm history of TBI and to classify injury severity. The OSU-TBI Worst Injury Score ranges from 1 to 5, with 1 indicating no history of TBI, 2 and 3 indicating mild TBI, 4 indicating moderate TBI, and 5 indicating severe TBI (33). These scores classified participants' injuries as mild or moderate–severe.

Medical Center Cohort

A demographic questionnaire captured age, gender, race (including Hispanic as an option), and highest level of education completed. History of TBI was confirmed via inclusion in a previous study requiring a diagnosis of concussion (e.g., mild TBI; Con-Tex study) or moderate–severe TBI (e.g., TBI Model Systems National Database study) or other clinical documentation as needed. Mild TBI was defined as a medical chart diagnosis of concussion with no known skull fracture or intracranial bleed; moderate–severe TBI was defined as documentation of at least one of the following: Glasgow Coma Scale score <13, loss of consciousness >30 min, post-traumatic amnesia >24 h, or positive neuroimaging.

Behavioral Assessment Screening Tool (BAST) in Both Cohorts

The BAST measures self-reported neurobehavioral symptoms in five domains: Negative Affect, Fatigue, Substance Abuse, Executive Function, and Impulsivity. It demonstrates good content validity and a multidimensional factor structure with good internal consistency reliabilities among community-dwelling adults with chronic TBI (30, 35). Subscale scores represent an average score for frequency of experiencing symptoms within each subscale, ranging from 1 (never) to 5 (very often).

Analyses

We calculated frequency and percentages of demographic characteristics and means and standard deviations for each of the BAST subscales within each cohort. To address the primary aim of the present study, we descriptively compared BAST subscale scores by cohort to examine cohort differences

and performed non-parametric tests for independent samples (Kruskal–Wallis, Mann–Whitney) to statistically test cohort differences. All analyses were performed using Statistical Packages for the Social Sciences (SPSS, v.24) software with a conservative overall significance level of $\alpha = 0.01$ to account for multiple testing.

RESULTS

Participants

National TBI Cohort

Of a total of $n = 263$ participants in the National TBI Cohort, $n = 211$ reported mild TBI and $n = 52$ reported moderate–severe TBI. **Table 1** presents demographic and neurobehavioral symptom data for participants in the National TBI Cohort.

Medical Center TBI Cohort

Of the 218 participants making up the Medical Center TBI Cohort, $n = 109$ were from Study 1, $n = 24$ were from Study 2, and $n = 85$ were from Study 3. **Table 1** presents demographic and neurobehavioral symptom data for participants in the Medical Center TBI Cohort.

Neurobehavioral Symptoms Group Comparisons

The National TBI Cohort reported significantly higher scores across all BAST subscales ($p < 0.001$) than the Medical Center TBI Cohort (see **Table 1**). **Table 2** presents neurobehavioral symptom data for participants in both cohorts broken down by gender and by educational attainment. In both cohorts, women reported higher Fatigue scores than men ($p < 0.01$). However, in the National TBI Cohort, men also reported significantly higher Substance abuse than women did ($p = 0.001$), and women reported significantly higher negative affect than men did ($p < 0.001$), which was not observed in the Medical Center TBI Cohort. In the Medical Center TBI Cohort, men reported more Impulsivity than women did ($p = 0.010$), which was not observed in the National TBI Cohort. There were no significant cohort differences in neurobehavioral symptoms by educational attainment (≥high school education vs. >high school education).

TABLE 1 | Characteristics and neurobehavioral symptoms in two English-speaking cohorts of community-dwelling adults with TBI.

Participant characteristics		National TBI cohort ($n = 263$)		Medical center TBI cohort ($n = 218$)	
		Mild TBI $n = 211$	**Moderate-severe TBI $n = 52$**	**Mild TBI $n = 85$**	**Moderate-severe TBI $n = 133$**
		***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Gender	Women	114 (54.0)	20 (38.5)	52 (61.2)	51 (38.3)
	Men	92 (43.6)	30 (57.7)	33 (38.8)	82 (61.7)
	Transgender/Other	5 (2.4)	2 (3.8)	0 (0)	0 (0)
Race	White	180 (85.3)	39 (75.0)	66 (77.5)	124 (93.2)
	Black/African American	11 (5.2)	4 (7.7)	14 (16.5)	7 (5.3)
	Asian	6 (2.8)	5 (9.6)	5 (5.9)	1 (0.8)
	American Indian/Alaskan native	4 (1.9)	1 (1.9)	0 (0)	0 (0)
	Native Hawaiian/Pacific Islander	1 (0.5)	2 (3.8)	0 (0)	0 (0)
	Other	7 (3.3)	1 (1.9)	0 (0)	1 (0.8)
	Unknown	2 (0.9)	0 (0)	0 (0)	0 (0)
Ethnicity	Hispanic	23 (10.9)	6 (11.5)	4 (4.7)	3 (12.5)
	Non-Hispanic	183 (86.7)	46 (88.5)	81 (95.3)	21 (15.8)
	Unknown	5 (2.4)	0 (0)	0 (0)	109 (82.0)
Education	≤High school	37 (17.5)	9 (17.3)	5 (5.9)	36 (27.1)
	>High school	174 (82.5)	43 (88.5)	80 (94.1)	97 (72.9)
		Mean (*SD*)	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**
Age (years)		40.55 (15.50)	44.15 (15.72)	43.25 (15.68)	47.42 (14.42)
Range		18-81	21-82	21-81	21-86
BAST Subscales	Negative affect	3.26 (0.75)	3.16 (0.69)	2.69 (0.72)	2.67 (0.73)
	Fatigue	3.16 (0.89)	3.07 (0.70)	2.99 (0.83)	2.66 (0.85)
	Executive function	2.27 (0.66)	2.40 (0.68)	2.11 (0.55)	2.15 (0.59)
	Impulsivity	2.30 (0.75)	2.44 (0.82)	1.84 (0.65)	2.08 (0.74)
	Substance abuse	1.83 (0.94)	2.10 (1.03)	1.13 (0.33)	1.33 (0.66)

All BAST Subscale values are mean (standard deviation) of the average score across items in each subscale. Data from the English-Speaking National Cohort were also published in Juengst et al. (32).

TABLE 2 | Neurobehavioral symptoms by gender and education in both TBI cohorts.

BAST subscale	National TBI cohort ($n = 263$)				Medical center TBI cohort ($n = 218$)			
	Mild TBI $n = 206$		Moderate-severe TBI $n = 50$		Mild TBI $n = 85$		Moderate-severe TBI $n = 133$	
	Women $n = 114$	Men $n = 92$	Women $n = 20$	Men $n = 30$	Women $n = 52$	Men $n = 33$	Women $n = 51$	Men $n = 82$
Negative affect	3.42 (0.74)	3.06 (0.71)	3.39 (0.67)	3.06 (0.66)	2.68 (0.73)	2.71 (0.70)	2.83 (0.77)	2.56 (0.69)
Fatigue	3.36 (0.90)	2.91 (0.08)	3.24 (0.76)	2.98 (0.12)	3.11 (0.79)	2.81 (0.86)	2.84 (0.84)	2.55 (0.85)
Executive function	2.22 (0.67)	2.34 (0.63)	2.45 (0.71)	2.40 (0.66)	2.09 (0.51)	2.15 (0.61)	2.14 (0.57)	2.16 (0.61)
Impulsivity	2.23 (0.76)	2.37 (0.08)	2.41 (0.58)	2.53 (0.17)	1.75 (0.62)	1.98 (0.68)	1.98 (0.62)	2.14 (0.73)
Substance Abuse	1.61 (0.82)	2.08 (0.99)	1.97 (1.00)	2.20 (1.10)	1.06 (0.19)	1.23 (0.46)	1.34 (0.69)	1.33 (0.65)
BAST subscale	**Mild TBI $n = 211$**		**Moderate-severe TBI $n = 52$**		**Mild TBI $n = 41$**		**Moderate-severe TBI $n = 177$**	
	≤HS $n = 37$	>HS $n = 174$	≤HS $n = 9$	>HS $n = 43$	≤HS $n = 5$	>HS $n = 36$	≤HS $n = 80$	>HS $n = 97$
Negative affect	3.32 (0.71)	3.25 (0.75)	3.32 (0.80)	3.12 (0.68)	2.86 (1.14)	2.68 (0.69)	2.82 (0.80)	2.61 (0.70)
Fatigue	3.14 (0.89)	3.16 (0.90)	3.22 (0.62)	3.04 (0.72)	3.30 (1.31)	2.97 (0.79)	2.74 (0.91)	2.63 (0.79)
Executive function	2.39 (0.64)	2.24 (0.66)	2.52 (0.64)	2.37 (0.69)	2.18 (0.74)	2.11 (0.54)	2.22 (0.64)	2.12 (0.57)
Impulsivity	2.31 (0.79)	2.29 (0.75)	2.31 (0.54)	2.47 (0.87)	2.05 (0.41)	1.83 (0.66)	2.13 (0.69)	2.06 (0.76)
Substance abuse	1.83 (1.01)	1.83 (0.92)	2.15 (1.03)	2.09 (1.05)	1.07 (0.15)	1.13 (0.34)	1.49 (0.95)	1.27 (0.52)

All values are mean (standard deviation) of the average score across items in each subscale. Individuals identifying as Transgender/Other for gender are not included in the table due to very small sample size when breaking down by injury severity (n = 5 mild TBI; n = 2 moderate-severe TBI) in the National TBI Cohort and no individuals identifying as Transgender/Other in the Medical Center TBI Cohort.

DISCUSSION

We identified symptom differences between two cohorts of individuals with TBI recruited from different sampling frames, demonstrating that individuals with TBI recruited through academic and clinical institutions may not be representative of individuals with TBI living across the United States. Across all symptom domains, those in the nationally representative sample reported more frequent neurobehavioral symptoms than those in the sample recruited through academic and clinical institutions. Racial and ethnic differences and geographic location as a proxy indicator of access to quality healthcare systems may explain the cohort differences we observed (14). Individuals with TBI living further from major medical centers not only have more pre- and post-injury comorbities, which can contribute to neurobehavioral symptoms (32), but also report more unmet service needs (28), suggesting that their underlying conditions are not adequately managed. In addition to the broader geographic representation in our National TBI Cohort, there was also a greater racial and ethnic diversity compared to our Medical Center Cohort. Prior work on racial and ethnic disparities after TBI suggests that factors associated with access to healthcare, including socioeconomic status, quality of education, access to care, quality of care, and transportation barriers (14), may explain differences in post-TBI functional outcomes.

We anticipated that educational attainment would partially explain these cohort differences, based on past literature (36–38), but we found no differences in neurobehavioral symptoms by educational attainment in either cohort, and on average, participants in both cohorts had relatively comparable rates of post-secondary education. However, there were differences in educational attainment when breaking each cohort down by injury severity. Those in the National Cohort who had a mild TBI were far less likely to have any post-secondary education than those in the Medical Center Cohort with a mild TBI, but those with a moderate–severe TBI in the National Cohort were more likely to have post-secondary education than those with moderate–severe TBI in the Medical Center Cohort. The potential protective effects of education may partially explain why those in the Medical Center Cohort with mild TBI reported fewer symptoms. More vulnerable individuals (e.g., lower education, lacking insurance) from minority groups may not recognize the need for medical care after a mild TBI or may not be able to allocate the limited resources available to them to address symptoms they view as mild (21). For those with a history of more severe injuries, the cognitive consequences of TBI may overshadow the protective effects of post-secondary education on neurobehavioral symptoms. For them, high-quality healthcare—especially early after moderate–severe TBI—may be a more important factor. Racial and ethnic minorities are less likely to receive inpatient rehabilitation after TBI (17), and when they do, the time to rehabilitation admission is longer compared to non-Hispanic white patients (21). Therefore, the more frequent neurobehavioral symptoms in the National Cohort participants with moderate–severe TBI, despite a greater proportion having completed post-secondary education,

may be a result of differential healthcare access, quality, and utilization.

Similar to past literature on gender differences in symptom reporting after TBI (12, 13), we found that women reported more fatigue symptoms than did men, and men reported more impulsivity and substance abuse symptoms than did women. However, other than the finding that women reported more fatigue than men did, these gender differences were not consistent across the two cohorts. The extent to which this is attributable to men representing a larger proportion of those with moderate–severe TBI vs. mild TBI and/or to the National TBI cohort including a substantially larger proportion of mild TBI than moderate–severe TBI remains unclear. Therefore, though notable cohort differences exist, the effect of the interaction between gender and cohort on neurobehavioral symptoms after TBI requires further study.

Comparing these two cohorts revealed the limitations inherent in the recruitment methods and catchment areas for a substantial proportion of the research published on chronic TBI, particularly with regard to representativeness. The Medical Center Cohort had a higher percentage of participants who were white, non-Hispanic, and, for those with mild TBI, had some post-secondary education. Though it represented participants recruited from two academic medical centers and two clinical rehabilitation centers across three geographically separated metropolitan areas in the United States, it did not have the same geographic coverage as the National TBI Cohort. Since the BAST yielded higher scores overall in the National TBI Cohort than the Medical Center Cohort, we strongly urge that meaningful within-person change scores, rather than hard cutoff scores, be established for clinical interpretation. Within-person change would be less prone than hard cutoff scores to external factors (e.g., access to healthcare, quality of education, etc.) that are difficult to quantify and adjust for in norm-based scores. Establishing within-person symptom variability at the individual level and defining meaningful change as that which falls outside of natural variability would most effectively account for the multitude of unmeasurable factors contributing to neurobehavioral symptoms. Future research should identify novel approaches to ensure valid and meaningful measurement of long-term outcomes and should identify modifiable barriers to quality care after TBI for individuals who are most vulnerable to healthcare disparities.

Limitations

The Medical Center Cohort comprised three distinctly different studies, with different inclusion and exclusion criteria, aims, and data collection methods, potentially introducing additional bias related to sample selection. Furthermore, we did not collect data on important factors that may explain differences in the two cohorts, including participants' access to healthcare, health and treatment history, and social support systems. Though we took multiple steps to ensure the validity of all data, data collected via anonymous survey are prone to bias and error. Most notable were differences between the two cohorts in identification, confirmation, and severity classification of TBI. While the Medical Center Cohort relied on medical documentation, the National Cohort relied on self-report via an electronic structured version of the OSU TBI asking questions about history of head injury via a variety of mechanisms, loss of consciousness (presence and duration), and experiencing a period of feeling dazed or confused after injury. Confirmation of injury and characterization of severity are determined by study investigators based on answers to these questions, following structured guidelines and scores for the OSU TBI (33, 34). However, despite efforts to ensure validity of self-reported TBI, differences in methodology between the cohorts introduces potential bias. Finally, the Medical Center Cohort included a larger proportion of individuals with moderate to severe TBI than the National Cohort, which was predominantly mild TBI. In the absence of measures to characterize cognitive ability and self-awareness, we cannot say with certainty whether the differences in self-reported symptoms are due to different symptom patterns based on injury severity, self-awareness differences (e.g., those with milder injuries may have better self-awareness of the symptoms they are experiencing), or other factors outside of injury that differed between cohorts.

CONCLUSIONS

Individuals with TBI connected to academic or clinical rehabilitation centers may systematically differ from the broader population of adults with TBI across the United States. Disparities in access to and utilization of healthcare services may contribute to more frequent and untreated neurobehavioral symptoms. Clinicians and researchers should take care when generalizing results from studies with non-representative samples, especially when establishing cutoff scores for patient-reported outcomes.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Texas Southwestern Medical Center, Baylor Scott & White Institute for Rehabilitation, and University of Pittsburgh. Participants provided informed consent to participate in these studies.

AUTHOR CONTRIBUTIONS

SJ was the senior author, principal investigator on two of the studies presented in this manuscript, and co-investigator on the two other studies presented. She was the primary author responsible for writing, conceptualization, and final decisions. AN contributed to data preparation, conducted extensive literature review, and drafted significant portions of the manuscript. LT collaborated with SJ in the initial study conceptualization, provided consultation on all statistical analysis as a statistician, and drafted significant portions of the methods and results. All authors have made significant contributions to

the conceptualization, interpretation, writing of this manuscript, and the study described herein and have read and approved the final manuscript.

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Theory of Mind Impairments Highlighted With an Ecological Performance-Based Test Indicate Behavioral Executive Deficits in Traumatic Brain Injury

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Background: In view of the recent literature, the negative impact of traumatic brain injury (TBI) on social cognition remains a debated issue. On one hand, a considerable number of studies reported significant impairments in emotion recognition, empathy, moral reasoning, social problem solving, and mentalizing or theory of mind (ToM) abilities in patients with TBI. On the other hand, the ecological validity of social cognition tasks is still a matter of concern and debate for clinicians and researchers.

Objectives: The objectives of the present study were 2-fold: (1) to assess social cognition in TBI with an ecological performance-based test which focuses on ToM ability, and (2) to study the relationship between performances on this task and behavioral disorders. To this end, 47 patients with moderate to severe TBI in the chronic stage were assessed with a ToM task, the Movie for the Assessment of Social Cognition (MASC), a film displaying social interactions in natural settings and asking for an evaluation of the emotions, thoughts, and intentions of the characters. Behavioral disorders were assessed with the Behavioral Dysexecutive Syndrome Inventory (BDSI), a structured interview of an informant in assessing changes compared with previous behavior in 12 domains.

Results: Patients were significantly less accurate in mental state attribution than a demographically matched group of 38 healthy control subjects. Significant others of patients also reported more behavioral executive problems than controls' relatives on most of the domains of the BDSI. In addition, social cognition performance in the MASC was significantly correlated with behavioral dysexecutive problems rated by proxies on the BDSI.

Conclusions: This study is the first to find association between impairments in mentalizing abilities in the MASC and behavioral impairments in patients with TBI, confirming the added value of this ecological task and that the recognition of social signals is a key element for adequate behavioral functioning.

Keywords: theory of mind, ecological assessment, behavioral dysexecutive disorders, traumatic brain injury, mentalizing abilities

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INTRODUCTION

The notion of social cognition embraces several subdomains and refers to all the socio-emotional abilities and experiences regulating the relationships between individuals and allowing the explanation of individual human behaviors or behaviors in a group (1, 2). A core component of social cognition is Theory of Mind (ToM), namely, the ability to attribute mental states to ourselves and to others to explain and predict behavior (3). Social cognitive neuroscience [see, for example, (4, 5)] has defined two main subcomponents of ToM, including cognitive ToM (referring to beliefs, thoughts, and intentions) and affective ToM (referring to emotions and feelings).

ToM is a component of social cognition that is of concern for adults who suffered traumatic brain injury (TBI) as, over the past few decades, a proliferation of research has shown that adults with moderate to severe TBI exhibited significant deficits on ToM tasks [for review, see (6)]. These deficits have been observed for both components of ToM, early after injury (7–9) and in the chronic stage (10–12). These patients have difficulty understanding that someone else may have a wrong belief (13), identifying what may be embarrassing in a situation (14), detecting the intentions behind someone's behavior (7), and inferring what a person may think or feel (15).

For the purpose of our work, it is important to emphasize that most of the studies on ToM in TBI have been conducted using static scenario-based tasks, such as stories based on false belief or understanding a faux pas (8, 12, 16) or cartoon sequences based on intention predictions (7), in which one or more characters are presented with limited contextual information and participants are required to infer the mental states of the character(s) presented. Photographs of the eye region of the face have also been used (7). Although these tasks have been very helpful to understand the basic functioning of ToM, they often fail to really challenge healthy human's mentalizing capacity in a way like what happens on everyday basis in real life (17, 18). More specifically, these tasks lack ecological validity as they require participants to use their ToM abilities in static situations that are oversimplified, often unimodal (verbal or visual), relying on few indicators or cues, and finally very different from real-life situations. According to Achim et al. (17), a better way to assess ecologically ToM abilities is to use videos as stimuli as they present situations in a more naturalistic way (multimodal and dynamic) than verbal or visual static tasks.

Moderate to severe TBI also causes significant behavioral changes that may severely impact participation (19), return to work (20), quality of life (21), and caregiver burden (22). According to a recent review by Milders (23), the incidence of these changes is between 25 and 88% for persons with moderate to severe TBI, with higher prevalence rates associated with more severe TBI. These behavioral changes mainly include behavioral executive disorders (19) with, for example, hypoactivity, anticipation difficulty, euphoria, hyperactivity, environmental dependency, anosognosia, confabulation, and sexual conduct disorders [see, for example, (21, 24) for a description of the characteristics of the behavioral dysexecutive syndrome in cohorts of patients with severe or moderate to severe TBI].

Since these behavioral dysexecutive disorders often involve inadequate emotional behaviors or sociopathic behaviors [see, for example, (25)], deficits in social cognition have been put forward by several authors as a possible underlying mechanism [see, for example, (14, 23)]. In line with this proposition, Spikman et al. (26) found that deficits in basic emotion recognition after moderate to severe TBI, a core component of social cognition abilities, were related with behavioral changes reported by significant others in the Dysexecutive Questionnaire (27), a 20-item questionnaire measuring a broad spectrum of behavioral dysexecutive disorders. Recently, Milders (23) reviewed 10 studies [including the study by (26)] that examined correlations between recognition of emotions (in faces, in faces and tone of voice, or in dynamic face and body postures) and post-injury behavior in TBI (self-ratings or informant ratings concerning social communication, social integration, social outcome, and behavior). Six studies reported that better emotion recognition was significantly associated with fewer behavioral problems in these patients. In four studies, correlations were not significant, but in the expected direction.

Studies examining the relationships between ToM impairments and behavioral dysexecutive disorders in TBI are even rarer, the first being led by Milders et al. (14). In a seminal work, Milders et al. studied the relationships between ToM perception (assessed with a verbal ToM test, the faux pas test), and proxy ratings of difficulties in social/emotional behavior following TBI [assessed with the Neuropsychology Behavior and Affect Profile; (28)] and failed to find association between these variables. In a second study combining scores from the faux pas test and the cartoon test (a visual ToM test), Milders et al. (29) found no significant association between ToM impairments and proxy ratings of post-TBI social and emotional behavior changes using the same questionnaire. Similarly, in a third study, May et al. (30) found no significant association between proxy ratings of social behavior (with the Dysexecutive Questionnaire) following TBI and performance on four tasks of intention inferences (the faux pas test, the hinting test, the ToM cartoon test, the cartoon predictions test). In his recent review of literature, Milders (23) identified three other studies that correlated ratings of behavior following TBI with ToM abilities. In the study by Struchen et al. (31), an association between the ability to identify inappropriate behavior in video vignettes of social situations and self-ratings of social integration was reported in a group of 184 patients with TBI. In the study by Ubukata et al. (32), no significant correlation between ToM abilities (mind in the eyes test and faux pas test) and social outcome appeared. Finally, in the study by Byom and Turkstra (33), the better use of words that refer to thoughts, feelings, or desires was associated with a better quality of social communication (as rated by an independent observer) in moderate to severe TBI.

To sum up, few studies have investigated the putative links between ToM deficits and behavioral impairments in TBI. The available results are rather unconvincing or contradictory. As mentioned above, this could be related to the fact that ToM tests may lack ecological validity and may not be suitable to provide answers to questions with respect to daily life problems. These inconsistent results can also be explained by the diversity

of questionnaires and the type of assessments (self-ratings vs. proxy ratings), the heterogeneity of samples (e.g., time since injury, number of participants), and the insufficient statistical power (23). Additionally, it should be noted that ToM ability is least routinely assessed than other processes of social cognition in clinical practice (34). Thus, additional studies are needed to support the evidence of an association between deficits in ToM and behavioral dysexecutive disorders. The present work is fully in line with this perspective. Our aim was to investigate whether ToM abilities, as measured with an ecological performance-based test, might be a predictor of behavioral dysexecutive deficits in patients who sustained a severe TBI, as measured by proxy ratings. We wanted to explore whether ToM impairments are related to behavioral dysexecutive disorders.

MATERIALS AND METHODS

Ethics Statement

This study was approved by the local ethical research committees and the independent protection of individuals committee of University Ouest II, Angers, on 25 January 2013, and authorized by the National Health Authority on 29 January 2013. Written and oral information was given to the participants and their proxies. Written consent was obtained from all participants (patients, proxies, and legal representatives) when appropriate.

Population

This work was part of AVEC-TC, a larger cohort study designed in our University Hospital to describe the treatment and management of individuals with moderate to severe TBI and the expertise of their proxies [see (24)]. In this cohort study, all patients with history of TBI using health or social services at the University Hospital of Angers, in local specialized rehabilitation or community-based facilities, or addressed to the investigators by the patient's family association, were screened for participation. Inclusion criteria in AVEC-TC were (1) existence of a moderate to severe TBI with an initial Glasgow Coma Scale (GCS) score of <13 and/or hospitalization for at least 48 h in intensive care; (2) participants were in the post-acute period (at least 3 months post-TBI); (3) participants were living in their own home or in a care facility; (4) with a proxy willing to participate in data collection and complete the behavioral evaluation. The proxy could be a relative, a friend, or a professional caregiver; (5) participants were aged between 18 and 65 years at the time of inclusion. Exclusion criteria included (1) non-traumatic acquired brain injuries, (2) mild TBI, and (3) speech or language impairments that would compromise the understanding of instruction and completion of the interviews and tasks. Additionally, in the present work, TBI patients with history of psychiatric problems were excluded.

All eligible participants were approached and asked to participate in AVEC-TC study. Data were collected via structured interviews. The participants and their proxies were convened by one of the investigators in a participating center. They were received together and then separately to complete questionnaires and tests. For professional caregivers, the questionnaires could be completed without the presence of an investigator and sent by mail.

The subgroup of patients with TBI who participated in our work included 47 individuals (29 males). Educational level ranged from 6 to 17 years of education [10.9 (2.8)]. Age at assessment ranged from 18 to 65 years [31.3 (10.5)], and age at injury ranged from 14 to 49 years [19.1 (4.9)]. The patients with TBI were, on average, 12.2 years post-injury at the time of the evaluation (SD = 10.21 years, range = 0.9–41 years). Mean coma duration was 18.2 (13.4) days (coma duration was not available in six cases), and mean post-traumatic amnesia duration was 42.6 (29.1) days (post-traumatic amnesia was not available for 11 cases). For 39 patients with TBI, GCS scores were available, ranging from 3 to 12, with a mean of 6.2 (2.2). At the time of the study, half of the patients with TBI (29/47) were in receipt of neuropsychological rehabilitation, but none of them was receiving or has received a rehabilitation program specifically focused on behavioral disorders. Forty patients with TBI were living at home, and the remaining patients lived in facilities specializing in the care of patients with brain damage.

Patients with TBI were compared to a group of 38 healthy control (HC) subjects (24 males) with a mean age of 31.2 years (range 19–57; SD 10.3) and a mean total year of education of 11.3 years (range 7–17; SD 2.3). All HC subjects were free of neurological and psychiatric illness and recruited from a database of volunteers.

ToM Task

ToM abilities were measured with the Movie for the Assessment of Social Cognition [MASC; (35)], translated and validated into French in a partnership between the team of Dr. Patricia Garel (Sainte-Justine University Hospital Montreal, Québec) and the team of Dr. Isabelle Amado (Centre Hospitalier Sainte-Anne, Service Hospitalo-Universitaire, Paris, France) [see (36)].

The MASC includes a wide range of contexts/situations requiring ToM ability (37) and meets the criteria of ecological validity for mentalizing tasks proposed by Achim et al. (17). It consists of a short film of 15 min which describes four young protagonists (two females and two males) spending an evening together (one can see them cooking, eating, and playing games together). The MASC has the advantage of integrating visual and auditory input channels and to request online inferences based on visual cues such as facial expressions, gestures, and body language, like in real-life situations. Another advantage of the MASC is that it investigates inference of emotions (affective ToM), thoughts, and intentions (cognitive ToM) with a single task using comparable situations. The video is stopped at 45 moments during the story, and the subject must answer questions concerning the mental states of one of the characters (emotional epistemic, volitional), as well as to questions ($n = 6$) concerning non-mental details depicted in the video which are used to control for memory and general comprehension abilities. According to Dziobek et al. (35), 17 items assess the inference of emotions, seven items assess the inference of thoughts, and 18 items assess the inference of intentions. A typical question for the category inference of emotion is: "What is Ben feeling?"; for the subscale thoughts: "What is Anna thinking?"; and for the

subscale intentions: "Why is Michaël saying this?" The subject must select his/her answers at the precise moment when the film is stopped among four possibilities: (1) correct answer (ToM), (2) "under-mentalizing" answer, (3) lack of mental state attribution answer (no ToM), and (4) "over-mentalizing" answer. Five main scores are derived from the MASC: (1) MASC sum of correct answers (maximum 45) as index of ToM performance (MASC ToM), three error scores; (2) "over-mentalizing" error score (Iper-ToM); (3) "under-mentalizing" error score (Ipo-ToM); (4) lack of ToM (No-ToM); and (5) score on control items (control score) as a measure of general comprehension ability (maximum six). Higher MASC ToM ccore and control score indicate better performance. Higher error scores (Iper-, Ipo-, and No-ToM) indicate lower performance. Administration of the tests takes between 30 and 45 min.

Many studies have shown that the MASC was a reliable and sensitive task for demonstrating subtle ToM impairments in individuals with social anxiety, body dysmorphic, or obsessive–compulsive disorders (38), or depressive subjects (39), in individuals with borderline traits (40), in adults with Asperger syndrome (35), and in patients with schizophrenia (36, 41). Studies in neurologic patients are rarer, with only two studies showing ToM impairments in multiple sclerosis (42, 43). Finally, Lecce et al. (37) have shown that older adults were less accurate in mental state attribution than young adults in the MASC, but not in more classical ToM tasks (strange stories, for example). The study herein is the first to use the MASC in a group of patients with TBI.

Behavioral Executive Functioning

Behavioral dysexecutive deficits were assessed by proxies using the Behavioral Dysexecutive Syndrome Inventory (BDSI). This questionnaire is a part of the GREFEX battery (19). It proposes a structured interview that assesses changes compared to premorbid behavior in 12 different domains: (1) reduction of activities (hypoactivity with apathy-aboulia, avolition); (2) difficulties for anticipation, planning, and initiation of activities; (3) disinterest and indifference to his/her own concern and others; (4) euphoria, joviality, emotional lability; (5) irritability, aggressiveness; (6) hyperactivity, distractibility, impulsivity; (7) stereotyped and perseverative behavior; (8) environmental dependency; (9) anosognosia–anosodiaphoria; (10) confabulations; (11) social behavior disorders; and (12) disorders of sexual, eating, and urinary behavior. For each domain, the proxy is asked to state if the behavior differs from the participant's pre-injury behavior. If positive, the proxy is asked to rate the severity (from 1 to 3: mild, moderate, or major), frequency of occurrence (from 1 to 4: from occasional to daily), and the burden induced by the behavior (resounding score). To be considered as dysexecutive, behavioral disorders should not have other causes (cognitive, psychiatric, or sensorimotor disorders) and must significantly change the activities of daily life, social life, or work compared to the pre-injury state. The informant had to rate the frequency and the severity of behavioral changes, thus providing an index (frequency × severity) for each behavioral domain. According to Godefroy et al. (19), a domain should be considered as positive if the index is >2 (5% cutoff), and subjects with at least three positive domains could be considered to have a behavioral dysexecutive syndrome.

Proxies were close family members (spouses, mothers/fathers, brothers/sisters, children) for 40 (85%) participants with TBI, friends for 4 (8.5%), and professional caregivers for 3 (6.5%). Professional caregivers were paramedical professionals and educational or social workers. Proxies were close family members for 33 (87%) HC subjects and friends for 5 (13%). Proxy raters were required to have known the patients with TBI or HC subjects for at least 2 years and to have observed them in social situations. Please note that given the unequal sample sizes across the types of raters and the weakness of the samples of friends and professional raters, it was not possible to analyze whether ratings of behavioral problems differed according to rater type.

RESULTS

Statistical Analyses

Tests for normality (Kolmogorov–Smirnov) indicated that the MASC subscores were normally distributed. Therefore, we used parametric tests (one-way and factorial ANOVAs) to evaluate differences between patients' performances with TBI and HC subjects for these scores. With significant factorial ANOVA results, *post-hoc* Scheffé tests were performed. As BDSI scores were non-normally distributed, we used non-parametric tests (Mann–Whitney *U* tests) to examine for behavioral differences between groups. Effect sizes (Cohen's *d*) were calculated for all comparisons between the groups. Regarding effect sizes for non-parametric statistics, as their estimates are known to be affected by departures from normality of variances, we followed the recommendations of Ivarsson et al. (44) [see also (45)] who suggested an effect size estimator for use in association with non-parametric statistics. To calculate the point–biserial correlation, these authors reported that the formula $rpb = z / \sqrt{N}$ could be used, with z being the value obtained from Mann–Whitney *U*-test and N being the sample size. Next, the traditional Cohen's d value is calculated with the formula $d = 2r/\sqrt{(1-r^2pb)}$. According to Cohen's (46) suggestions (small: $d = 0.20$; medium: $d = 0.50$; large: $d = 0.80$), generally large effect sizes were found for significant differences between groups, whereas non-significant results were associated with small effect sizes. Spearman correlations were calculated to determine relationships between MASC scores and tBDSI-informant scores and between MASC scores and clinical data. Frequencies were compared with chi-square test. All statistical analyses were carried out using Statistica 9.0 (StatSoft. Inc. Tulsa, USA). The significance threshold was set at $p < 0.01$ rather than $p < 0.05$ to reduce the possibility of type I errors.

Sociodemographic Characteristics

Chi-square and ANOVAs showed that patient and control groups were matched for sex ($\chi^2 = 0.36$, $p = 0.54$), age [$F_{(1,83)} = 0.01$, $p = 0.91$] and educational level [$F_{(1,83)} = 0.35$, $p = 0.55$].

MASC Scores

Performances in the MASC are given in **Table 1**. There was no difference between groups for the MASC control score [$F_{(1,83)} = 1.01$, $p = 0.31$]. Correct answers for the attribution

TABLE 1 | Performances of patients with TBI and HC subjects on the MASC (raw scores).

	Patients with TBI ($n = 47$) mean (SD)	HC subjects ($n = 38$) mean (SD)	p*	d**
MASC ToM Score correct (0–45)	23.1 (2.6)	31.8 (3.5)	<0.0001	1.40
MASC Control Score correct (0–6)	4.9 (1.2)	5.1 (0.8)	0.31	0.09
MASC error scores				
MASC Iper-ToM errors (0–45)	5.9 (2.5)	5.2 (2.1)	0.18	0.14
MASC Ipo-ToM errors (0–45)	13.1 (2.1)	5.4 (1.6)	<0.0001	2.06
MASC No-ToM errors (0–45)	2.8 (1.4)	2.6 (1.4)	0.34	0.09

Mean and standard deviation (SD) of the various scores of the MASC test are indicated in the table. MASC ToM Score total number of correct answers, MASC Control Score number of correct answers for control questions, MASC Iper-ToM number of exceeding ToM errors, MASC Ipo-Tom number of less ToM errors, MASC No-ToM number of No-ToM errors.

**Overall analysis with ANOVA, **effect sizes (Cohen's d).*

of mental status (MASC ToM Score) were different between the two groups, with fewer correct answers in patients with TBI compared to HC subjects [$F_{(1,83)} = 171.36$, $p < 0.0001$]. The effect size was very large according to Cohen (46).

Given that the MASC allows one to examine different aspects of mental state inference in a more ecological context, we were also interested in investigating whether TBI specifically impacted on the type of subcomponents of ToM in this context. To do that, we ran a two-way ANOVA on the percentage of correct answer on the MASC, with group (patients with TBI vs. HC subjects) as the between-subjects factor and type of mental state inference (emotion vs. thought vs. intention) as a the within-subjects factor. The main effect of group was highly significant [$F_{(1,83)} = 174.84$; $p < 0.0001$]. Patients with TBI had lower percentages of correct inferences (mean 51.3%) than HC subjects (mean 70.6%) on the MASC across conditions. The main effects of type of mental state inference [$F_{(1,83)} = 0.04$; $p = 0.95$] and the population × type of mental state inference interaction [$F_{(2,166)} = 0.54$; $p = 0.58$] were not significant, showing that, independent of group, no differences on percentages of correct answers were found between inference of emotions (mean 65.4%), thoughts (mean 65.8%), and intentions (mean 64.7%) on the MASC. The absence of interaction reflected similar differences between proportions of correct answers for inferences of emotions, thoughts, and intentions in patients with TBI (thoughts vs. emotions, mean difference = 0.2%; thoughts vs. intentions, 1.9%; intentions vs. emotions, 2.1%) and HC subjects (thoughts vs. emotions, 1.2%; thoughts vs. intentions, 0.7%; intentions vs. emotions, 1.8%).

We were finally interested in investigating whether TBI specifically impacted on the type of errors made in attributing mental states. To this end, we performed a two-way ANOVA with group (patients with TBI vs. HC subjects) as a between-subjects factor and error type (Iper-ToM, Ipo-ToM, no-ToM) as a within-subject factor. Results showed a significant interaction between group and error type ($F_{(2,166)} = 50.63$, $p < 0.0001$). We explored this interaction through pairwise comparisons. Results showed that patients with TBI reported a lower percentage of Iper-ToM errors ($p < 0.0001$; mean for patients with TBI, 27.1%; mean for HC subjects, 39.5%) and had higher percentages of Ipo-ToM ($p < 0.0001$; mean for patients with TBI, 59.8%; mean for HC subjects, 40.8%). No-ToM errors were less frequent ($p < 0.0001$) in patients with TBI (mean 13.0) than in HC subjects (mean 19.5). It is also important to note that within both groups, there were differences between all the error types, with the Ipo-ToM being the most frequent, the Iper-ToM being of medium frequency, and the No-ToM error being the least frequent. In the group of patients with TBI, the difference between percentages of Iper-ToM, Hypo-ToM, and No-ToM errors were significant (all $p < 0.0001$). In HC subjects, the percentages of Iper-ToM and Ipo-ToM errors did not significantly differ ($p = 0.91$), and both were significantly higher than the percentage of no-ToM errors (all $p \leq 0.0001$).

Behavioral Dysexecutive Syndrome Inventory

On the BDSI, higher scores equate to more behavioral problems. The proxies/professional indexes (frequency × severity) appeared higher in all behavioral domains, with significant differences between patients with TBI and HC subjects for 10 indexes (see **Table 2**): reduction of activities ($U = 291.5$, $z = -5.31$, $p < 0.0001$), anticipation–planning–initiation disorders ($U = 374.5$, $z = -4.58$, $p < 0.0001$), disinterest and indifference ($U = 439.5$, $z = -4.00$, $p < 0.0001$), euphoria–joviality–emotional lability ($U = 617$, $z = -2.43$, $p = 0.01$), irritability–aggressiveness ($U = 399.5$, $z = -4.36$, $p < 0.0001$), hyperactivity–distractibility–impulsivity ($U = 535$, $z = -3.16$, $p = 0.0001$), stereotyped and perseverative behavior ($U = 468.5$, $z = -3.75$, $p = 0.0001$), anosognosia–anosodiaphoria ($U = 401.5$, $z = -4.34$, $p < 0.0001$), social behavior disorders ($U = 437$, $z = -4.03$, $p < 0.0001$), and disorders of sexual–eating–urinary behavior ($U = 589$, $z = -2.68$, $p = 0.007$). The differences did not reach significance for environmental dependency ($U = 829$, $z = -0.56$, $p = 0.57$) and confabulations ($U = 839$, $z = -0.47$, $p < 0.63$). The effect sizes for the significant differences ranged from −0.54 to −1.41, which can be classified as moderate to very large according to Cohen (46).

Using a 5% cutoff (19), behavioral indexes were impaired in 10–62% of patients with TBI. Frequency of impairment ≥50% was observed for reduction of activities (62%), anosognosia–anosodiaphoria (56%), and anticipation–planning–initiation disorders (54%). Frequency of impairment ≤50% was observed for disinterest and indifference (49%), social behavior disorders (49%), irritability–aggressiveness (47%), stereotyped and perseverative behavior (43%), disorders of sexual–eating–urinary behavior (35%), euphoria–joviality–emotional lability (32%), hyperactivity–distractibility–impulsivity (32%), environmental dependency (10%), and confabulations (10%). Thirty-seven patients with TBI (79%) had a behavioral dysexecutive syndrome.

TABLE 2 | Proxies'/professionals' indexes (frequency × severity) for patients with TBI and HC subjects on the behavioral domains of the BDSI (mean and standard deviation).

	Patients with TBI ($n = 47$) mean (SD)	HC subjects ($n = 38$) mean (SD)	p*	d**
Reduction of activities	5.5 (4.4)	0.3 (0.6)	<0.0001	−1.41
Anticipation–planning–initiation disorders	4.2 (3.7)	0.9 (1.8)	<0.0001	−1.14
Disinterest and indifference	3.1 (3.3)	(0.5) (1.4)	<0.0001	−0.96
Euphoria–joviality–emotional lability	1.7 (2.4)	0.3 (0.7)	0.01	−0.54
Irritability–aggressiveness	2.9 (3.0)	0.3 (0.8)	<0.0001	−1.07
Hyperactivity–distractibility–impulsivity	2.5 (3.5)	0.3 (0.9)	0.0004	−0.73
Stereotyped and perseverative behavior	3.1 (4.1)	0.2 (0.7)	<0.0001	−0.89
Environmental dependency	0.2 (0.6)	0.1 (0.4)	0.57	−0.12
Anosognosia–anosodiaphoria	4.7 (4.7)	0.3 (1.0)	<0.0001	−1.06
Confabulations	0.2 (0.4)	0.1 (0.4)	0.63	−0.10
Social behavior disorders	3.7 (4.3)	0 (0)	<0.0001	−0.97
Disorders of sexual–eating–urinary behavior	1.5 (2.5)	0 (0)	0.007	−0.60

*Mann –Whitney U-tests, **effect sizes (Cohen's d).

Correlations

For patients, the correlations (Spearman correlation coefficients) between medical data and the performance on the MASC (MASC ToM Score) were non-significant: duration of coma (rho = 0.24, $p = 0.15$), post-traumatic amnesia (rho = 0.31, $p = 0.07$), and mean time since injury (rho = −0.007, $p = 0.96$).

We investigated the relationships between ToM impairments and behavioral dysexecutive disorders in patients. Since we did not find any effect of the specific subdomains of ToM (emotions, thoughts intentions) on the performance of patients, and to limit the number of correlations, we were only interested in the relationships between the total number of correct answers on the MASC and BDSI indexes. As expected, significant correlations were observed between MASC and BDSI scores. More specifically, in patients with TBI, there were significant correlations between the MASC ToM Score and proxies'/professionals' indexes for reduction of activities (rho = −0.46; $p = 0.0009$), disinterest and indifference (rho = −0.47; $p = 0.0007$), hyperactivity–distractibility–impulsivity (rho = −0.45; $p = 0.001$), irritability–aggressiveness (rho = −0.34; $p = 0.01$), and social behavior disorders (rho = −0.44; $p = 0.0001$). All correlations were negative, indicating that poorer performance on the MASC corresponded with more problems on the BDSI. Nevertheless, no significant correlation emerged between MASC ToM Score and BDSI proxies'/professionals' indexes for anticipation–planning–initiation disorders (rho = −0.25; $p = 0.08$), euphoria–joviality–emotional lability (rho = 0.006; $p = 0.96$), stereotyped and perseverative behavior (rho = −0.08; $p = 0.55$), environmental dependency (rho = 0.07; $p = 0.61$), anosognosia–anosodiaphoria (rho = −0.08; $p = 0.55$), confabulations (rho = −0.01; $p = 0.92$), and disorders of sexual–eating–urinary behavior (rho = 0.12; $p = 0.39$).

In HC subjects, correlations between the MASC ToM Score and proxies' indexes were significant for social behavior disorders (rho = 0.50; $p = 0.002$), euphoria–joviality–emotional lability (rho = 0.42; $p = 0.009$), stereotyped and perseverative behavior (rho = 0.45; $p = 0.005$), anosognosia–anosodiaphoria (rho = 43; $p = 0.008$), and disorders of sexual–eating–urinary behavior (rho = 0.50; $p = 0.002$). Correlations were non-significant for reduction of activities (rho = 0.01; $p = 0.91$), disinterest and indifference (rho = 0.19; $p = 0.23$), hyperactivity–distractibility–impulsivity (rho = 0.29; $p = 0.07$), irritability–aggressiveness (rho = 0.24; $p = 0.13$), anticipation–planning–initiation disorders (rho = 0.06; $p = 0.68$), environmental dependency (rho = 37; $p = 0.02$), and confabulations (rho = 26; $p = 0.10$).

DISCUSSION

To the best of our knowledge, this is the first study that found ToM impairments after moderate to severe TBI using the MASC, a single dynamic task that featured a combination of verbal and visual content in a social context, to conduct an ecologically valid assessment of daily life social interactions. We confirm that the French version of the MASC is a sensitive test in capturing deficits in attribution of mental states. In line with previous findings, we observed that patients with moderate to severe TBI were significantly impaired for both affective (emotions inferences) and cognitive (inference of thoughts and intentions) components of ToM abilities when compared to a matched group of HC subjects. In both groups, there was no significant difference between the proportions of correct answers for cognitive and affective items. In line with past literature, this could suggest an equivalent decline in ToM performances in TBI (7, 10–12, 26). The fact that patients show difficulties in the attribution of the right mental states to others in such a real-life social scenario suggests that their decay in ToM performance is not simply due to the limited ecological validity of the tasks usually used. This decay can be considered as a genuine deficit that reflects a real decline in ToM abilities.

In this work, the use of the MASC to investigate ToM also allowed us to examine the type of errors that patients with TBI make when they wrongly attribute mental states to others. Our results revealed that they produce more Ipo-ToM and No-ToM errors than HC subjects, suggesting that moderate to severe TBI reduces mental state attribution. Under-mentalizing behaviors have also been observed in patients with multiple sclerosis (42, 43), suggesting that brain lesions

diminish the abilities to attribute mental states to others. This profile of errors (lack of ToM inferences) has also been observed among patients with psychiatric disorders, such as patients with schizophrenic and autism spectrum disorders [see, for example, (36, 41)]. Our findings that moderate to severe TBI is characterized by insufficient mental state reasoning for emotions, thoughts, and intentions in ecological settings add to the existing literature on the presence of social cognition impairments in TBI and expand the profile of TBI. These results can be helpful to orient treatments of ToM impairments. These rehabilitation programs must focus on mental states attribution rather than on an inclination to "over-mentalize," which seems to be not the principal ToM deficits of patients with TBI, contrary to some psychotic spectrum conditions such as schizophrenia [e.g., (47)].

In line with previous findings, and according to the BDSI, more than three quarters of the sample (79%) had dysexecutive behavioral disorders, which is consistent with past findings. In their study, Azouvi et al. (21) found a prevalence of 81.5% of behavioral dysexecutive syndrome in a population of individuals with severe TBI, with a very similar distribution in the sub-domains of BDSI. Indeed we also observed that reduction of activities, anticipation–planning–initiation disorders, and anosognosia–anosodiaphoria were the most frequent behavioral changes after TBI (frequency of impairment $\geq$50%). In our study, disinterest and indifference, social behavior disorders, and irritability–aggressiveness were also very frequent behavioral changes reported by professionals and closest relatives as compared to pre-injury. Estimated rates for disinterest and indifference [49% in this study and 46.3% in the study by Azouvi et al. (21)] or irritability–aggressiveness (47 vs. 42.6%) were close to those found by Azouvi et al. (21). For social behavior disorders, the estimated rate was higher in our study (49 vs. 24.1%).

Our study is very clearly in favor of the idea that deficits in social cognition may contribute, at least in part, to executive behavioral disorders. In fact, we observed important relationships between the MASC ToM score and various indexes of the BDSI (reduction of activities, disinterest and indifference, hyperactivity–distractibility–impulsivity, irritability–aggressiveness, and social behavior disorders). Our results are in line with what was expected in this work and are clearly in favor of the idea that the MASC is an ecologically valid test of social cognition impairments. Our results are also in accordance with the models of social cognition that propose that social cognition abilities are important for social functioning and that impairments in social cognition abilities may result in difficulties with social behavior (48–50).

Reduction of activities (hypoactivity with apathy–aboulia, avolition) was associated with ToM performance. This finding suggests that hypoactivity also reduces mental state attribution. In the present study, the fact that patients presented under-mentalizing behaviors (producing more Hypo- and No-ToM errors than HC subjects and more Hypo- and No-ToM errors than Hyper-ToM errors) is consistent with this proposition. In addition, neuropsychological investigations have already documented an association between apathetic manifestations and low performance on tests assessing ToM abilities in some neurological and psychiatric disorders (51–56). Disinterest and indifference are associated with impairment in ToM. This finding suggests that these manifestations prevent patients from taking into consideration others' points of view and is consistent with the view that the ability to move from an egocentric perspective to an exocentric perspective is crucial in ToM (57). The fact that hyperactivity–distractibility–impulsivity and irritability–aggressiveness were associated with ToM performance could be interpreted in the same way. These behavioral manifestations surely have to do with an inability to break away from environmental stimuli (hyperactivity–distractibility–impulsivity) or from personal preoccupations (irritability–aggressiveness) or, in other words, with an inability to disengage from environmental stimuli and one's own perspective and consider others' points of view. Finally, attribution of mental states was found to be strongly associated with social behavior disorders. This finding suggests that impaired inference of emotions, thoughts, and intentions contributes to the occurrence of social behavior disorders. Under-mentalizing could lead patients to misunderstand the internal mental states of their interlocutors and therefore not to adapt and/or adjust their own behaviors toward these interlocutors.

In the control group, correlations between MASC ToM score and behavioral ratings do not went in the same direction, confirming that social cognition indexes sometimes behave differently in the presence/absence of TBI. Significant coefficients were positive, which makes them difficult to interpret: the better the HC subjects were at the MASC, the more their relatives considered they had behavioral problems. In addition, with respect to significant correlations, no proxies of control subjects reported social behavioral disorders (0//38) and disorders of sexual–eating–urinary behaviors (0/38). Concerning the three other BDSI indexes (joviality–emotional lability, stereotyped and perseverative behavior, anosognosia–anosodiaphoria), only two to five proxies scored them differently from 0. Regarding these elements, the validity of these correlations and their meaningfulness seem questionable to us.

Some limitations of our study must be considered. Firstly, there may have been some selection bias due to our inclusion criteria. Indeed we enrolled patients living in the care or with a proxy. Participants who were not in contact with health institutions or who were living alone were not included. This may have led to an overestimation or an underestimation of behavioral dysexecutive impairments. However, this type of bias is inherent to the assessment of individuals with brain lesions. Secondly, we could not guarantee that all participants were free from personality problems that might have influenced their ToM abilities, such as a lack of empathy, an inability to understand other people's emotions, or alexithymia. However, none of the patients that we included had a history of psychiatric problems according to medical records and anamnesis with patients and proxies. Thirdly, in the same vein, 11 patients incurred their injuries before age 18 (between 14 and 16 years), at a developmental milestone that could have impacted upon the development of social to us emotional skills [see,

for example, (58)]. So we could not guarantee that all patients with TBI were free from developmental problems that might influence their ToM performance. Fourthly, we did not propose a neuropsychological assessment to patients with TBI, in particular of non-social cognitive functions frequently impaired in this population: speed of information processing, attention, executive functions, and working memory. Impairments of these functions in the group of patients with TBI could potentially contribute to their poorer performance on the MASC since it is a multimodal and dynamic ToM task presumed to strongly appeal to cognitive skills. However, this was not possible in the AVEC-TC study. In addition, we did not consider this possibility very likely since results of several studies document a possible dissociation between cognitive impairment after severe acquired brain injury and social cognition deficits [see, for example, (7, 59–62)]. In this regard, some authors have suggested that ToM and other cognitive domains should be considered as independent systems (7, 8, 63). In line with this argument, Laillier et al. (64) found that cognitive measures partially mediated the age effect on cognitive and affective ToM performances in healthy subjects using the MASC. In addition, dissociations between cognitive and behavioral assessments have been found in TBI with patients performing within the normal range on the cognitive battery while demonstrating significant behavioral changes (21). Such findings indicate that cognitive and behavioral dysexecutive syndromes may be dissociated (19) and support the hypothesis that behavioral disorders cannot always be explained by cognitive disorders. Another limitation concerns the fact that ToM was assessed with a single video-based task, namely, the MASC. Other tasks of this type are available [see, for example, the Video Social Inference Task; (65, 66)]. We selected this test because of its ecological validity, its ability to examine different subdomains of ToM as well as its high sensitivity. However, we must keep in mind that the MASC remains an offline paradigm of social cognition that focuses on ToM from an observer's rather than from an interactor's point of view [for the distinction between online and offline tasks of social cognition, see (67)]. In future works, adding online paradigms of ToM, with direct person-to-person interactions [for an example of online ToM tasks, see (68)], would surely enhance further ecological validity and help us to better understand the nature of the links between ToM deficits and social behavioral disorder in TBI. A final point concerns the use of an informant assessment of behavioral disorders. Indeed hetero-evaluations may lead to overestimation or underestimation of behavioral problems, depending, for example, on the burden induced by the behavior (69). However, behavioral disorders are often more precisely described by proxies than by patients because of anosognosia. In the same logic, it may well be that assessment of behavioral problems could naturally differ depending on the type of rater employed (i.e., relative vs. professional), suggesting that, in future studies on the relations between ToM deficits and behavioral dysexecutive disorders, it would be certainly important to obtain behavioral assessments provided from different types of raters. If the correlations we found in this work were confirmed through behavioral assessments made by different types of raters, they would have more weight. The opposite would allow us to bring nuances to our conclusions.

In conclusion, the main findings of the present study revealed that patients with moderate to severe TBI were less accurate to attribute emotions, thoughts, or intentions to characters than HC subjects in an ecologically valid ToM task. They also made more Hypo-ToM and No-ToM errors than HC subjects. ToM deficits were linked to behavioral executive dysfunctions. Our data are consistent with the view that ToM impairments might be a predictor of behavioral dysexecutive deficits in patients who sustained a moderate to severe TBI However, further investigations with larger samples of persons with TBI will be necessary to determine if the relationship between affective and cognitive ToM impairments and behavioral changes in a patient is causal or not.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the local ethical research committees and the independent protection of individuals committee of University Ouest II, Angers, on 25 January 2013, and authorized by the National Health Authority on 29 January 2013. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PA, VS, and MD conceived and planned the experiment. VS and MD recruited participants. MH was involved in acquisition of data. PA, MH, and JB processed the experimental data and performed the analysis. PA wrote the manuscript with assistance from JB, MD, VS, and CV. PA supervised the project. All authors commented on the manuscript.

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REVIEW
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Sex and Gender Differences in Emotion Recognition and Theory of Mind After TBI: A Narrative Review and Directions for Future Research

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A growing body of literature has examined sex differences in a variety of outcomes from moderate-severe traumatic brain injury (TBI), including outcomes for social functioning. Social functioning is an area in which adults with TBI have significant long-term challenges (1–4), and a better understanding of sex and gender differences in this domain may have a significant clinical impact. This paper presents a brief narrative review of current evidence regarding sex differences in one aspect of social functioning in adults with TBI: social cognition, specifically affect recognition and Theory of Mind (ToM). Data from typical adults and adults with TBI are considered in the broader context of common stereotypes about social skills and behaviors in men vs. women. We then discuss considerations for future research on sex- and gender-based differences in social cognition in TBI, and in adults more generally.

Keywords: social cognition, gender, sex difference, brain injury, adult

INTRODUCTION

In 2001, a U.S. Institute of Medicine (IOM) report (5) stated that sex-based differences were a priority area for all research on human health. This statement was a change for clinical and basic TBI research, which had focused mostly on men for both epidemiological reasons (higher prevalence in males) and practical reasons (e.g., effects of fluctuating hormone levels). In the years since the IOM report, studies have examined sex differences in a variety of TBI outcomes, including outcomes for social functioning. Social functioning is arguably the area in which adults with TBI have the greatest long-term challenges (1–3, 6, 7). Thus, a better understanding of sex differences in this domain may have a significant clinical impact.

This paper begins with a brief narrative review of research on sex differences in one aspect of social functioning in adults with moderate-severe TBI: social cognition, defined broadly as the processes used to decode the social world (8). The review focuses on two aspects of social cognition that have been studied in TBI: recognition of emotions from facial affect; and Theory of Mind

(ToM), the ability to attribute mental states to oneself and others, and use that information to make predictions about others' actions (9). We chose these two aspects of social cognition because they have been linked to broader social outcomes like quality of life and social reintegration, both conceptually (10–12), and empirically (13–20). We consider data from typical adults and adults with TBI, in the broader context of common stereotypes about social skills and behaviors in men vs. women. The remaining sections of the paper discuss considerations for future research on sex-based differences in social cognition in TBI, and in adults more generally.

As defined by the Institute of Medicine, sex is the "classification of living things, generally as male or female based on their reproductive organs and functions assigned by a chromosomal complement;" whereas gender "refers to a person's self-representation as male or female, or how that person is responded to by social institutions based on the individual's gender presentation" [(5), p. 1]. Most of the studies we reviewed focused on biological sex, and we indicate gender where it was clearly defined. We return to the issue of sex vs. gender in our hypotheses about social cognition after TBI. We use the terms "female" and "woman" interchangeably, typically the former as an adjective and the latter as a noun.

SEX DIFFERENCES IN SOCIAL COGNITION IN TYPICAL ADULTS

Nowhere are there more profound and enduring stereotypes for men and women than in "social thinking." The stereotype that women are better at "reading" other people has some empirical support. Several studies have reported a female advantage in emotion recognition in typical adults (21–27), beginning in childhood and persisting throughout life (28–30). Differences generally are small (e.g., accounting for <10% of variance in scores) and are mostly for threat-related affective displays. Analysis of 14,000 samples of written and spoken language showed that women also used more emotion words (e.g., happy, certainty, nervous, and hate) than men, and fewer swear words (31), although again effect sizes were small [i.e., 10–22].

One challenge in generalizing study results to real life is that most stimuli were some version of the iconic six "basic" emotions popularized by Ekman in the 1970s (32). These canonical stimuli do not capture the subtle and dynamic affect displays encountered in everyday social interactions, and women might be better at reading the latter. Consistent with this notion, Hoffman et al. (33) found sex-based differences only for morphed images that were 40–70% of the full facial expression, with no difference for full facial expressions. These findings replicated findings from a previous morph study from the same lab (34) and suggest that more subtle tests might reveal larger sex-based differences.

A second challenge to generalizing results is that participants in prior work were typically given unlimited time to respond. In everyday life, facial and vocal affect displays change in milliseconds (35), a phenomenon Ekman (36) himself exploited in his "lie detection" research, and women may be better at making those quick judgements (24). Again, consistent with that notion, women had higher accuracy scores than men when stimuli were presented at very brief durations (24), identified emotions earlier in the series of morphs than men (34), and overall responded more quickly than men for both morphs and static images (Byom et al., in preparation). Taken together, these results suggest that women are faster at recognizing emotions overall, especially when affective displays are subtle.

By contrast to the literature on emotion recognition, only a few studies have addressed sex differences in ToM or "cognitive empathy" (37). The typical experimental ToM task is a version of the classic False Belief task (38) or Piaget's (39) perspective-taking task, in which the participant must recognize that one actor in a scenario has access to information that the other does not. Most studies have reported no significant difference on ToM tasks between men and women (37, 40–42) or girls and boys [e.g., (43)]; although some have reported trends for better scores in females [e.g., (44)]. ToM findings contrast with those on emotional empathy (feeling the feelings of others), for which women are thought to have an advantage (45).

Taken together, studies of typical adults suggest a female advantage for recognizing emotions in affective displays of others, albeit a small advantage and mostly on subtle or complex tasks. There is no evidence of sex differences in ToM, at least on classic perspective-taking tasks, despite the public perception that women are better at "mindreading."

SEX DIFFERENCES IN SOCIAL COGNITION IN ADULTS WITH TBI

To identify articles for the narrative review of TBI studies, we searched PubMed, PsychInfo, CINAHL, and Web of Science using the search string: (emotion recognition OR affect recognition) AND (social cognition OR theory of mind) AND traumatic brain injury AND (sex difference or gender difference), with the limits of *human* and *adult*. We excluded review papers and theoretical papers that did not contain data, studies of children, and studies that included men and women with TBI but did not report their scores separately.

The literature search yielded three papers (26, 46, 47) that examined sex differences in social cognition in adults with TBI. Two additional papers reported scores separately for women and men with TBI (41, 42). A third reported sex differences in the context of other findings (48), but the clinical group included participants with etiologies other than TBI, and scores for the TBI subgroup were not reported separately. Thus, that paper was excluded. Of the five studies summarized here, two tested emotion recognition and three tested Theory of Mind. Study characteristics are summarized in **Table 1**.

Rigon et al. (26) compared men and women on recognition of both the iconic Ekman-type emotions and also morphing images, which yield accuracy scores according to both emotion type and intensity. The authors found a small but significant female advantage on both tasks. This advantage was independent of emotion type or intensity, injury characteristics such as chronicity and severity, cognitive ability as indexed by neuropsychological test scores, or lesion laterality. Overall, scores

TABLE 1 | Summary of studies reviewed.

References	TBI group	Comparison group	Constructs assessed	Main findings
Rigon et al. (26)	53 adults with moderate-severe TBI (28 females)	49 adults (22 females) matched demographically by group	Emotion recognition from static and morphed faces	No significant sex difference on static images; significant group X sex interaction for morphed images, with lowest scores in males with TBI
Turkstra et al. (41)	58 adults with moderate-severe TBI (24 females)	66 adults matched demographically by group	ToM in video vignettes	No significant sex difference
Turkstra (42)	19 adults with moderate-severe TBI (9 females)	19 adults matched for age and sex	ToM in still images and video vignettes	Significant group X sex interaction for still images, with lowest scores in males with TBI; trend toward significant interaction on video vignettes, with lowest scores in males with TBI
Zupan et al. (46)	160 adults with moderate-severe TBI (44 females)	Published norms	Affective empathy and ToM (perspective taking) in written statements	No significant difference in proportion of men vs. women with TBI who scored in the impaired range compared to norms
Zupan et al. (47)	160 adults with severe TBI (116 males)	None	Facial and vocal affect recognition from static images, ToM (emotional inferencing) in movie scenes	Significantly higher scores in women for vocal affect and ToM; trend for women to have higher scores for facial affect

ToM, Theory of mind; TBI, traumatic brain injury.

of females with TBI were not significantly different from those of age-, race-, and education-matched uninjured peers; whereas males with TBI were significantly less accurate than either uninjured men and women or women with TBI. It is noteworthy that Schmidt et al. (49) found similar results in children with TBI, i.e., higher emotion recognition scores in girls with TBI than boys. The authors hypothesized that this difference might reflect the "small but statistically significant" female advantage in typical development.

Zupan et al. (50) administered two affect tests to compare men and women with TBI: a basic facial and vocal affect recognition test, and a task the authors developed to test inference of emotions from video clips Women were more accurate on two of the three tasks—vocal affect recognition and emotional inference—with small to moderate effect sizes. Contrasting with the findings of Rigon and colleagues, there was no significant sex difference in facial affect recognition, which the authors hypothesized might reflect the prolonged stimulus exposure in their task (i.e., previous studies of typical adults showed that men were as accurate as women when response demands were lower). Interestingly, women were more accurate than men at recognizing fear in faces, sadness in voices, and both fear and sadness from stories; while there were no significant differences in accuracy for angry or happy stimuli. These emotion-specific findings are consistent with overall trends in data on emotion recognition in adults, as fear in particular is difficult to differentiate from surprise or sadness, particularly when participants are asked make judgements early in the temporal evolution of an emotional expression (51).

Léveillé et al. (52) reported emotion recognition scores for male and female athletes with a history of two or more concussions, compared to athletes with no concussion history. This study was initially excluded because the focus of the review was moderate-severe TBI, but the task was similar to the morph task described in Rigon et al. (26), so results might provide an informative comparison. Results were similar to those of Rigon et al.: a main effect of group and a group X sex interaction, with higher scores overall in women and disproportionately lower scores in men with a concussion history. Emotion-specific findings also were replicated, with fear having the lowest accuracy and highest intensity threshold for detection.

Zupan et al. (46) compared men and women with TBI on a self-report measure of perspective taking, in which participants are asked how well they are described by each of a series of statements (e.g., "I try to look at everybody's side of a disagreement before I make a decision"). Scores for both men and women were significantly lower than norms for the measure, a comparable percent of participants of each sex were classified as "impaired" according to those norms, and there was no significant difference in total scores between men and women. Close others also rated each participants' empathy. Men significantly under-rated their problems relative to ratings of their close others, whereas there was no significant difference between self- and others' ratings for women. Seventy-eight percent of all close others for both groups were women, a potential source of observer bias we will return to later in this paper.

Turkstra (42) compared men and women with TBI to uninjured peers on a ToM test, and replicated the study in a subsequent sample (41). Participants watched brief video vignettes of social interactions and made ToM judgements about actors in the videos. In the initial study, there was a significant group X sex interaction, with women performing better overall and disproportionately lower scores in men with TBI. The follow-up study, however, showed no significant effect of sex or group X sex interaction, although women had higher scores than men. It is not clear why results of the two studies differed. In both studies, TBI and uninjured comparison participants were matched for age, race, education, and sociodemographic factors; participants were drawn from the same general pool of Midwestern adults; and adults in both studies had moderate-severe injuries. It is not possible to directly compare cognitive status between the two

samples as the tests differed, but in both cases participants with TBI had significantly lower scores than uninjured peers. Future research may clarify whether there truly is no difference or if a difference is only present on certain tasks.

Overall, while the rationale for studying sex-based differences in social cognition after TBI is strong, the literature is sparse, results are mixed, and effect sizes are generally small. In the remainder of this paper, we discuss directions for the future and some reasons why research in this area is challenging.

CONSIDERATIONS FOR RESEARCH ON SEX-BASED DIFFERENCES IN SOCIAL COGNITION IN TBI

The current state of the science on sex-based differences in social cognition, along with our own reflections on sex and gender in social cognition, have led us to a few considerations for future work in this area.

Social Cognition May Be Related to Gender as Well as (or Instead of) Biological Sex

Up to this point we have focused on sex (the biological construct), but gender also may play a role in social cognition. Gender, while typically rooted in biology, is a social construct. It includes "how you, in your head, define your gender, based on how much you align (or don't align) with what you understand to be the options for gender" (53). Thus, while sex is typically binary, gender is on a continuum and may be fluid. Gender includes one's internal representation in relation to gender norms, how one expresses gender through outward appearance, and the roles one takes in social contexts, all of which may be fluid and dynamic (53).

We began thinking about gender as a factor in outcome in part because of the variability within each sex in our studies [e.g., (42)] and others' [e.g., (54, 55)]; and in part because of evidence of gender differences in cognitive functions linked to social cognition, particularly executive functions (EFs) (56, 57). Research on sex differences in EFs has been mixed but results from self-report EF scales have hinted at gender effects. For example, Norvilitis and Reid (58) asked 234 university students to complete a self-assessment of gender, the Bem Sex-Role Inventory (BSRI) (59), discussed in detail below) and the Executive Function Scale (60), an EF self-report measure. The authors found that, controlling for biological sex, masculine BSRI scores were positively correlated with self-reported EFs. Similarly, Turkstra et al. (61) administered the BSRI and the Behavior Rating Scale of Executive Function-Adult version (BRIEF-A) (62) to 53 adults with TBI (23 females) and 49 uninjured adults (29 females), and found that a significant amount of variance in BRIEF scores in both groups were accounted for by self-reported masculinity ($t = -4.57$, $p < .001$), but not biological sex ($t = 0.96$, $p = .33$) or self-reported femininity ($t = -0.41$, $p = 0.68$). These early findings raised questions about the role of gender as a predictor of behavioral outcome after TBI, and also how self-identity as a man or woman might differ from self-described gender role in social contexts.

Our first barrier to studying gender was that the terms are often used interchangeably. Indeed, confusion of the terms sex and gender is a key barrier in research on sex-based differences in general (5, 63). In TBI, it is almost impossible to identify the influence of gender on outcomes because the terms are used so inconsistently in the scientific literature. To illustrate, we searched PubMed publications for the past 5 years using the keywords "gender," "social communication," and "human." We retrieved 85 articles, and in all but three the word *gender* referred to biological sex. Some authors stated that they categorized sex using self-report questionnaires or hospital records, but most did not state their methods, which likely means that they either based their categorization on participants' responses to a multiple-choice question (e.g., *Circle one: M F*) or judged sex based on appearance, which is linked to gender not sex (53). It may be, then, that one factor confounding results in the literature on "sex-based differences after TBI" is the conflation of biological sex and gender.

Although there have been no studies of gender and social cognition, a few researchers have examined gender identity related to social functioning after TBI (64–68), and findings are informative for future social cognition studies. In a study of 33 males in the chronic stage after TBI (65), Schopp and colleagues found a significant correlation between some aspects of self-reported conformity to masculine gender roles (e.g., valuing winning) and outcomes such as earning, but most gender role variables were not significantly related to outcome variables. The highest correlation was between earnings post-injury and self-reported conformity to male violence norms, defined as the "tendency to utilize or value violence and beliefs that violence is sometimes required and justified" [(65), p. 1158]. The findings must be interpreted with caution, however, as results for 13 gender variables were correlated with four outcome variables in a sample of 33 participants, thus the analysis had a high risk of Type I error (finding differences where none exist).

Gutman and Napier-Klemic (69) conducted in-depth interviews with two men and two women with TBI to explore gender identity and gender role changes post-injury. The women reported less impaired internal gender identification while the men reported a sense of inadequacy in their gender role. In both cases, perceptions about gender role appeared to be related to the ability to participate in pre-injury activities that defined their masculine or feminine role. The authors interpreted this relationship as lack of participation causing perceived role changes; but impairments in social cognition skills needed for these "gendered" activities also could have been a contributing factor.

Alston, Jones and Curtin (70) conducted in-depth interviews of 11 women and 21 men with TBI in Australia. Narratives emerging from the in-depth interviews of women included themes related to power, control, the body and self-image, and the gendered nature of caretaking. The authors noted that outcomes after TBI reflected broader gender-linked trends in society, e.g., women reported increased self-consciousness about their bodies and body image post-injury, almost half of the women reported being a victim of financial abuse by people close to them, and only four of the women reported being cared for by a family member.

These results show the impact of societal expectations and the reality of gender influences on everyday life.

While gender identification is a critical variable in research, measuring it has proven to be a challenge. The BSRI (59) is perhaps the most consistently used tool, and its challenges illustrate the broader challenges of measuring gender in research. The BSRI is based on social constructs of femaleness or maleness, mostly in Western culture, and reflects links between the experience of gender and the person's social context (71). The premise underlying the BSRI is that each of us have both masculine and feminine personality characteristics and that gender-typing depends on the balance between these characteristics. The BSRI is comprised of a list of 60 personality characteristics grouped into three categories based on ratings by 100 undergraduate students in the 1960s (50 self-identified as women, 50 as men): 20 masculine characteristics, 20 feminine characteristics, and 20 neutral characteristics. The author categorized a characteristic as masculine or feminine if male and female judges agreed that it was more desirable for one sex or the other. Masculine characteristics include items such as *assertive* and *strong personality*, and feminine characteristics include items such as *compassionate* and *soft spoken*. Neutral items were those independently judged by men and women to be no more desirable for one sex than the other, and judged as equally desirable by men and women raters. Of the neutral group, 10 items were rated as highly desirable for anyone (e.g., *tactful*, *friendly*) and 10 were rated as highly undesirable (e.g., *conceited*, *unpredictable*).

To administer the BSRI, the experimenter asks respondents to indicate how well each characteristic describes them on a seven-point scale from 1 (never or almost never true) to 7 (always or almost always true). Each person receives a masculinity score, a femininity score, and an androgyny score. The androgyny score is calculated as the Student's *t*-ratio for the difference between the masculinity and femininity scores, i.e., the absolute difference between masculinity and femininity normalized with respect to the standard deviations of that participant's masculinity and femininity scores. Using the androgyny score, the individual is typed as masculine, feminine, or androgynous.

The first potential critique of the BSRI is that it is extremely dated. As one might expect, a 2006 study of undergraduate students did find some changes (72): stereotypic desirable behaviors for men again aligned with traditionally masculine traits such as *has a strong will*, *very active*, and *knows the way of the world*; but socially desirable behaviors for women included not only traditionally feminine traits such as *very understanding of others*, *very considerate of others*, and *very aware of feelings of others*, but also traditionally masculine traits such as *strong*, *independent*, and *enjoys a challenge*. Similar findings were reported by in three other studies at around the same time (73–75). These results suggest that male stereotypes have changed relatively little over time, at least until the early 2000s, whereas female stereotypes have expanded to include both masculine and feminine traits.

The BSRI, like other gender role and gender identity scales that rely on *a priori* social judgments [e.g., the Personal Attribute Questionnaire (76, 77)], also has been criticized for limitations in construct validity (78), and there has been debate about the scale factor structure, particularly the masculine factor (79–81). Nevertheless, the BSRI remains the most common measure of gender role in health-related research and is one metric to consider when evaluating gender. Whatever the tool used, measuring gender is clearly different from measuring biological sex.

To Capture Sex-Based Differences in Social Cognition, We Need More Sensitive and Realistic Experimental Tasks and Larger, Representative Samples

Results of emotion recognition research strongly suggest that most research stimuli do not include the subtle and rapidly changing affect cues for which women might have a marked advantage. Research is critically needed in this area, not only to characterize sex differences but also predict how social cognition impairments will manifest in everyday life for people with TBI. Video assessments such as The Awareness of Social Inference Test (82) and morph tasks such as the Emotion Recognition Test (22, 83) are a step toward analysis of in-the-moment affect recognition, but finer-grained measures and more complex stimuli are needed.

Sex-based differences also may be missed when samples include too few women or are generally underpowered. Women often are unrepresented in studies of TBI and some samples are composed entirely of men [e.g., Vietnam Head Injury Project (84)]. When samples are not well-balanced for sex, it may be difficult or impossible to detect meaningful and statistically significant sex differences. Even when samples do contain men and women, the data are seldom stratified by sex. Despite the well-documented heterogeneity in deficit profile and outcome following TBI, samples in TBI studies remain small. To detect reliable sex differences in social cognition, or in any domain, samples need to be considerably larger and efforts must be made to have more balanced samples with regard to sex.

Most Clinical Data Are From Self-Ratings, Which Are Prone to Stereotype Bias

Social communication, by definition, is communication in a social context and thus is subject to stereotypes about roles and behaviors. One's concept of maleness and femaleness is used to create standards of masculine and feminine gender-roles against which one perceives, categorizes, and evaluates their own behavior and personality and the behavior and personality of others (59), and this relationship is as true for social behaviors as it is for other domains. In other words, it's not just the person's ability but also what society expects of that person based on gender norms. A well-known example from the popular press is the observation by Tannen (85) that women use social interactions to build consensus or share thoughts and feelings, show more listening behavior and less interrupting in conversations, and show more self-disclosure and openness in their talk. While Tannen's observations were not experimentally derived, the general patterns have been confirmed

empirically [e.g., (86)], and the notion of sex-based differences in communication "style" has become part of our culture. Thus, a person with TBI has a double challenge: to perform according to his or her own gendered expectations and to meet expectations of others.

To explore how expectations *of* and *for* men and women might differ today, Stafslien and Turkstra (under review) asked 68 university undergraduates (34 self-identified as women, 34 as men) to identify acceptable behaviors for men and women using the LaTrobe Communication Questionnaire (LCQ), a well-validated questionnaire for evaluating social communication in adults with TBI (87). Participants were asked to rate how much of a problem each LCQ behavior would be if a woman displayed it vs. if a man did. Items were rated as not a problem at all (1), sometimes a problem (2), often a problem (3), or always a problem (4). Mean scores for each item were calculated for women vs. men raters. Items with mean ratings of 2.0 or higher were considered to indicate a problem behavior, and we compared items with high mean scores between male and female raters for the "if a woman did it" and "if a man did it" versions of the LCQ.

Two findings of the Stafslien and Turkstra study were notable. First, male and female raters agreed on six LCQ items that were problems for anyone, male or female (e.g., giving inaccurate information, not knowing when to talk and when to listen, not putting ideas together in a logical way). These items correspond to typical social communication problems in adults with TBI, supporting the ecological validity of the LCQ. Two items were rated by both men and women as problematic if shown by a woman but not a man (using vague or empty words or repeating oneself in conversation), and one if shown by a man but not a woman (saying something rude or embarrassing). Second, women raters identified 23 items overall as problematic if shown by either a man or a woman, and men identified 17. That is, women appeared to have less tolerance for violations of common social behaviors. These results suggested that standards for social cognition might be higher for women, particularly for women who display socially stereotypical feminine behavior, and that women might be harsher judges of social behavior in others. They also raise questions about bias in research and clinical assessment results when "other" raters are caregivers, who most often are women [e.g., (88)].

A HYPOTHESIS FOR FUTURE STUDY

Current data suggest that women have a small but significant advantage on social cognition tasks, an advantage that is most evident when stimuli are subtle and complex. There also are hints that men may be more vulnerable to TBI-related impairments in social cognition, but results are inconsistent. Societal expectations play a critical role in this relationship, particularly given evidence that social stereotypes about sex differences far exceed effect sizes in empirical studies.

We propose that social cognitive abilities and societal expectations interact over time in development and after injury, as shown in **Figure 1**. Women are shown as having a slight advantage in social cognition from childhood, and perhaps more "resistance" to TBI effects (at least for the types of stimuli typically used in research), but the range of acceptable behavior for women is narrower than the range for men; thus, women might see themselves—and others around them might see them—as less skilled in traditional female roles. Men are shown as starting out with slightly less skill in social cognition, and again potentially being more vulnerable to TBI effects, but this is offset somewhat by the broader range of acceptable behavior for men. The result of this interaction might be a difference between one person's test scores, self-ratings of social functioning, and ratings by close others. We have omitted gender from the figure because there are no data, but emphasize that gender must be considered in this model.

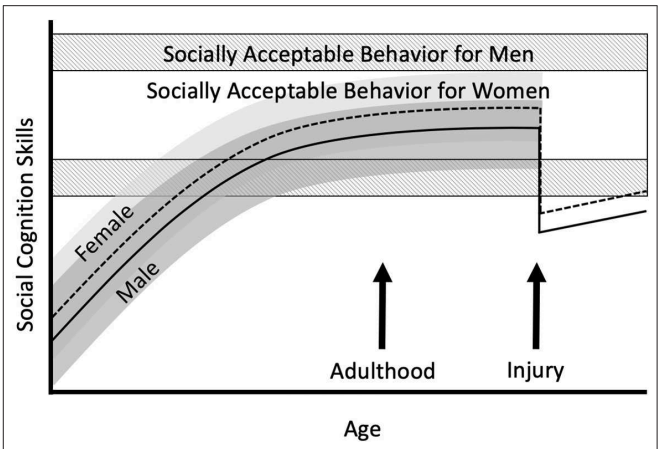

FIGURE 1 | Hypothesized relationships among social development, societal expectations, and effects of TBI in adulthood for men and women.

The model in **Figure 1** depicts injury sustained in young or middle adulthood. Equally critical are effects of injury in childhood and in older adulthood. The importance of understanding sex differences at these life stages is supported by emerging evidence of pediatric TBI effects on social cognition and communication (89, 90), and sex differences in outcome from pediatric TBI more broadly; and evidence of persistent social problems in older adults (91).

IMPLICATIONS FOR CLINICAL INTERVENTION

Current gaps in knowledge have several implications for clinical intervention. First, raters must consider their own potential bias in assessment, such as judging behaviors based on social stereotypes (e.g., "that's typical male behavior"). Second, clinicians must consider not only test or questionnaire results, but also the patient's gender identity—i.e., alignment with gendered roles of that person's social context. Patients might not spontaneously offer those perceptions, but they are important for treatment. Third, as part of patient-centered care, it is important to know what that individual's gender role, identity, and expression were pre-injury, as that will influence treatment

goals and expectations for that person. Finally, it is possible that women and men (or relatively male or female persons) respond differently to treatment, which may have confounded previously reported treatment study results. This was the case for Babbage et al. (92), who initially found no significant benefit of a story-based affective intervention in adults with TBI (93), but later discovered that the subgroup of women did indeed show treatment effects. The potential interaction of TBI and sex (or gender) in treatment must be addressed in future studies.

CONCLUSIONS

In summary, social functioning may be the most common and consequential area of long-term deficit for individuals with TBI, affecting all aspects of life. It is also a common target for treatment. Understanding how sex and gender play a role in social functioning, including social cognition, will advance our knowledge about social functioning after TBI, and help identify meaningful and effective intervention methods.

AUTHOR CONTRIBUTIONS

LT is the senior researcher on this team, led much of the work cited, and led writing of the manuscript. BM was co-investigator on the work cited and analyzed sex-based data for studies cited. CR completed the review of sex differences in emotion recognition. ED conducted the research on perceptions of sex differences and completed the review of sex differences in perception of social behavior. EH and ER completed the review of sex differences in executive functions, and introduced the concept of gender identity vs. expression. MD was co-investigator on the work cited here and led analysis of sex differences in emotion recognition after TBI.

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Visual Behavior, Pupil Dilation, and Ability to Identify Emotions From Facial Expressions After Stroke

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Social cognition is the innate human ability to interpret the emotional state of others from contextual verbal and non-verbal information, and to self-regulate accordingly. Facial expressions are one of the most relevant sources of non-verbal communication, and their interpretation has been extensively investigated in the literature, using both behavioral and physiological measures, such as those derived from visual activity and visual responses. The decoding of facial expressions of emotion is performed by conscious and unconscious cognitive processes that involve a complex brain network that can be damaged after cerebrovascular accidents. A diminished ability to identify facial expressions of emotion has been reported after stroke, which has traditionally been attributed to impaired emotional processing. While this can be true, an alteration in visual behavior after brain injury could also negatively contribute to this ability. This study investigated the accuracy, distribution of responses, visual behavior, and pupil dilation of individuals with stroke while identifying emotional facial expressions. Our results corroborated impaired performance after stroke and exhibited decreased attention to the eyes, evidenced by a diminished time and number of fixations made in this area in comparison to healthy subjects and comparable pupil dilation. The differences in visual behavior reached statistical significance in some emotions when comparing individuals with stroke with impaired performance with healthy subjects, but not when individuals post-stroke with comparable performance were considered. The performance dependence of visual behavior, although not determinant, might indicate that altered visual behavior could be a negatively contributing factor for emotion recognition from facial expressions.

Keywords: social cognition, theory of mind, facial expressions, emotion, visual behavior, gaze, pupil dilation, stroke

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INTRODUCTION

Social cognition is the innate human ability to interpret others' feelings and emotions and to regulate one's own behavior accordingly (1). This ability involves a combination of conscious and unconscious processes that facilitate social behavior and has supported human evolution from our ape-like ancestors to our current status as humans (2). Both verbal and non-verbal forms of communication during social interaction are intertwined and reinforced to enable an interpretation of the social context. Body posture (3) and movements (4) and, especially, facial expressions (5, 6) are common sources of non-verbal information that allow us to identify, and discriminate between,

to a certain degree, the emotional states of others. Specifically, the ability to recognize emotional expressions on faces has been repeatedly investigated in the literature, evidencing certain universal patterns across cultures (7), ages (8), and sex (9). The recording and analysis of eye movements and gaze patterns through eye-tracking technology have provided cognitive neuroscientists with insights into both the cognitive and physiological processing of visual information (10), which is especially interesting in terms of investigating the ability to recognize facial expression of emotion. Thus, eye-tracking studies have consistently shown that the eyes, mouth, and nose are the most thoroughly explored facial structures involved in scrutinizing emotional expressions (11–13). Moreover, the visual exploration of these areas has been shown to be dependent on the expressed emotion (13, 14), its intensity (11), the visual perspective of the face (15), or the resolution (12) and size of the visual stimuli (16). Apart from visual behavior, eye-tracking technology also allows the temporal variation of pupil size to be registered. Pupil dilation is controlled by both the sympathetic and parasympathetic nervous system (17) in response not only to light changes (18), but also to cognitive processes that involve alertness (19), memory (20), language (21), decision making (22), and emotional processing (18, 23–27). In the latter category, variations in pupil size have been described during the visualization of pictures with emotional attributes in comparison to neutral pictures (24, 26), and similar results have been reported with auditory stimulation (23). Importantly, pupil dilation has been related to an increase in sympathetic activity during emotional processing (24).

The acquisition, processing, and recognition of emotional information from faces involve a complex network of peripheral and central systems. In addition to the visual cortex and cortical association areas, which are commonly involved in the processing of visual information (17, 28), other brain regions, such as the fusiform face area in the ventral temporal lobes, are recruited when a human face is within sight (29). Other structures, such as the inferior occipital gyrus, the superior temporal sulcus (30), and the amygdala (31), are likewise engaged in the decoding of emotional information. The distributed nature of this brain circuitry is particularly vulnerable to both focal and diffuse injuries, such as those derived from cerebrovascular and traumatic accidents, which is supported by the high incidence of impairment in the ability to discriminate among emotions after an injury to the brain (32–44). The great majority of studies on facial emotion recognition have focused on individuals with traumatic brain injury (35–42), and have evidenced an apparent increased difficulty to recognize negative expressions, such as anger, disgust, sadness, or fear (35). Fewer, but still a substantial number of, studies have investigated this ability after stroke (34, 43–45), showing worsened performance in those subjects with lesions in the right hemisphere (34). Concurrent with impaired performance, altered visual exploration behavior has also been reported after brain injuries of different severity (46, 47).

The clinical relevance of difficulties in identifying facial expressions relies on its association with different neurobehavioral symptoms that range from changes in personality (32–42) to impaired self-awareness (48), which can negatively impact social integration (49, 50). These sequelae and other neurobehavioral changes after an acquired brain injury may complicate the quality of life of both the patients and their caregivers (51).

The diminished ability to identify facial expression of emotions after brain lesions has traditionally been explained by an impaired emotional processing (33); however, alterations in visual exploration could bias the integration of visual information and, consequently, have an additional negative effect on the performance of emotional tasks. While this hypothesis has been investigated in other pathologies with associated social cognition deficits, such as schizophrenia (52) and autism spectrum disorders (53), its plausibility after cerebrovascular injury is still unknown.

In light of the existing evidence, we hypothesized that individuals with stroke would perform poorly in comparison to healthy subjects at identifying emotions from facial expressions, and that this effect would also be revealed when considering individual emotions separately. We additionally hypothesized that impaired performance after stroke could be partially explained by an altered visual exploration of the face, and evidenced by an altered variation in pupil dilation. Consequently, the objectives of this study were to investigate the accuracy of the performance, the visual behavior, and pupil dilation of a sample of individuals with stroke during the identification of emotional facial expressions.

METHODS

Participants

A convenience sample of individuals with stroke were recruited from the outpatient unit of the neurorehabilitation service of Vithas Hospital Valencia al Mar (València, Spain), Vithas Hospital Aguas Vivas (Carcaixent, Spain), and the Brain Injury Center of Vithas Vinalopó (Elx, Spain). The inclusion criteria in this group were diagnosis of stroke confirmed by CT and/or MRI, aged over 18 years, with a fairly good cognitive condition, as defined by scores above 23 in the Mini-Mental State Examination (54), and the ability to follow instructions, as defined by scores above 45 in the receptive language index of the Mississippi Aphasia Screening Test (55). Individuals were excluded if they had disabling visual deficits, such as hemianopsia or impaired visual acuity, which would prevent appropriate visual stimulation and interaction. An additional group of healthy subjects, over 18 years of age, with no known cognitive or psychiatric impairments, were enrolled as controls.

A total of 111 individuals, 46 with stroke and 65 healthy controls, participated in the study. The group of individuals with stroke—either ischemic ($n = 18$) or hemorrhagic ($n = 28$)—consisted of 23 women and 23 men with a median time since injury of 428.0 (222–678) days and a median age of 53.5 (44–58) years. The control group consisted of 35 women and 30 men, with a median age of 48 (30–79) years. No significant differences were found in any demographic variable between these groups (**Table 1**).

All subjects who satisfied the inclusion criteria and accepted the terms of participation in the study provided informed

TABLE 1 | Characteristics of healthy subjects and individuals with stroke.

	Healthy subjects	Individuals with stroke	Significance
Sex (*n*, %)			$p = 0.836$
Women	35 (53.8%)	23 (50.0%)	
Men	30 (46.2%)	23 (50.0%)	
Age (years)	48.0 (36–62)	53.5 (44–58)	$p = 0.382$
Etiology (*n*, %)	–		–
Ischemic		18 (39.1%)[a]	
TACI		9 (47.4%)[b]	
PACI		5 (26.3%)[b]	
LACI		5 (26.3%)[b]	
Hemorrhagic		28 (60.9%)[a]	
Localization of the injury (*n*, %)	–		–
Right anterior circulation		20 (43.5%)	
Left anterior circulation		17 (37.0%)	
Posterior circulation		9 (19.5%)	
Time since injury (days)	–	428.0 (222–678)	–
Visual perception and cognition	–		–
Letter cancelation test (*n*)		10.0 (10–10)	
Wechsler Memory Scale IV			
Visual reproduction		8.0 (7–9)	
Rey–Osterrieth complex figure copy		32.0 (30–34)	
Color trail test			
Part A (s)		52.0 (38–68)	
Part B (s)		110.0 (80.5–138)	
Wechsler Adult Intelligence Scale IV			
Symbol search		19.50 (14.25–26)	
Matrix reasoning		17.5 (12–22)	

Demographic and clinical characteristics of healthy participants and individuals with a stroke. TACI, Total anterior circulation infarcts; PACI, Partial anterior circulation infarcts; LACI, Lacunar circulation infarcts. Age, time since injury, and performance in the neuropsychological tests are expressed in terms of median and interquartile range.

[a] *Percentage of all participants with stroke.*

[b] *Percentage of participants with ischemic stroke.*

written consent before enrolment. Ethical approval for this study was obtained from the Ethics Committees of the clinical institutions involved.

Instrumentation

Gaze behavior and pupil dilation was estimated using a Tobii TX300 screen-based eye tracker (Tobii AB, Stockholm, Sweden). This device captures gaze data from the corneal reflection of emitted IR light at 300 Hz. The system includes a 23″ screen, with a resolution of 1,920 × 1,080 pixels, which provides visual stimulation, and an eye-tracking unit, which includes an array of IR illuminators (transmitters) and sensors (receptors). In addition, the eye tracker is controlled by a dedicated computer, which incorporates a secondary screen that allows the trial to be managed and supervise without the visual stimulation being interfered with.

Visual stimuli were designed using Tobii Studio 3.2.1 (Tobii AB, Stockholm, Sweden). These consisted of 28 images extracted from the Karolinska Directed Emotional Faces database (56). The images illustrated four subjects—two men and two women—randomly selected from a list of 70 available people. The images reflected facial expressions of fear, anger, disgust, happiness, sadness, surprise, or an absence of emotion (neutrality). The images were displayed in the center of the screen, covering its entire height, which resulted in a picture size of 21 × 28 cm. The remaining areas of the screen were black. It was reported that the minimum time to explore the entire face is 4 s (57). Taking this into account, the stimuli were designed to be displayed in a randomized order for a 5-s period, 1 s longer than the minimum time period necessary to explore the entire face (57), during which gaze behavior and pupil dilation were recorded. Before each image was shown, a black screen was displayed for 500 ms to provide a subtractive baseline correction (58). After each image was shown, a thumbnail of the picture, along with seven words corresponding to the seven possible emotions, were displayed for a maximum of 30 s.

Procedure

The experiment took place in a dedicated, quiet room in one of the three clinical facilities, which was free of distractors and had controlled lighting conditions. The same experimenter conducted the study at all three sites. The participants were

briefly introduced to the task, and were then asked to sit comfortably in a chair facing toward the eye tracker, with their head at an approximate distance of 65 cm from the screen. The eye tracker was calibrated for each participant. After the calibration process, the accuracy of the calibration was experimentally determined, using the deviation between target points on the screen and superimposed estimated fixation points. If the accuracy proved insufficient, the calibration process was repeated. Once the calibration was successful, the experiment was started. The participants were asked to stare at the faces that appeared on the screen for 5 s and then to identify the emotion that, according to their criteria, best matched each facial expression, and to choose this from the seven words shown on the screen. The participants were asked to name the emotion, and the experimenter noted down each answer and then continued the study. If the participants were not able to answer in 30 s, that picture was considered unanswered and the experiment continued. Consequently, the total duration of the study, without considering the calibration process, varied according to the time each participant needed to identify each emotion.

The participants were also assessed using a battery of neuropsychological tests that evaluated the cognitive abilities that involved their visual perceptive skills. This assessment included the letter cancelation test, the visual reproduction subtest of the Wechsler Memory Scale IV, the Rey–Osterrieth complex figure, the color trail test, and the symbol search and matrix reasoning subtests of the Wechsler Adult Intelligence Scale IV.

Data Analysis

The accuracy in identifying the emotions from the facial expressions was estimated as a percentage of the correct identifications of each emotion, as in previous works (8, 11, 12, 15, 16). According to this value, two subgroups of the individuals with stroke were determined—those with comparable performance to the healthy individuals (those with an equal or better performance than the median performance of the healthy controls) or those with poorer performance than the healthy subjects (those with poorer performance than the median performance of the healthy controls).

Gaze behavior was defined in terms of the number of fixations—also known as fixation count—and the total time spent—also known as total fixation duration—on the eyes, nose, and mouth, which, as mentioned above, have been identified as being the most representative areas involved in a visual scan of the face (11, 12, 14, 15, 59). These areas were manually defined for each visual stimulus image, in accordance with previous studies (11, 12, 15, 59). The averaged pupil diameter variation was also extracted, as in previous studies (18, 60, 61). The results of all the eye-tracking measures represent the averaged behavior of both eyes. Finally, performance at identifying emotions from facial expressions was defined as the percentage of correct identifications.

Prior to the computation of pupil dilation, the pupil data were pre-processed, as follows. First, those images or baselines that presented a ratio of missing data >50% in either eye were discarded (23, 60, 62, 63). Second, the first 2 s of the stimuli were also discarded to remove the initial pupil contraction (60). Third, the non-physiological variations in pupil size, identified as those changes occurring at a faster rate than 5 mm/s, were removed. Fourth, the remaining time windows of missing data were linearly interpolated (23, 62, 63). Fifth, the time series were low-pass filtered at 8.3 Hz to reveal the low-frequency trend (23, 62). Finally, variations in pupil size were obtained through subtractive baseline correction, in which pupil size is converted to an absolute difference from baseline pupil size to that during the stimuli (corrected pupil size = pupil size – baseline) (58).

Differences between the groups of participants, in terms of demographic and clinical variables, visual behavior, and performance, were investigated using independent-sample Mann–Whitney *U* tests, except for sex distribution, etiology, and laterality of injury, which were investigated using chi-squared tests. The level of alpha was set to 0.05 for all analyses.

Data regarding fixation duration, fixation count, and pupil dilation were extracted using Tobii Studio 3.2.1. Signal processing was performed using MATLAB 2018b (MathWorks Inc., MA, USA). The statistical analyses were performed using SPSS for Windows v.22 (IBM, Armonk, NY, USA).

RESULTS

Accuracy

The accuracy in identifying facial expressions of emotion showed significant differences between the individuals with stroke and the healthy subjects, with the former showing decreased accuracy ($p = 0.012$) (**Figure 1**). The detrimental effect of a cerebrovascular accident incident was consistent for all emotions, but was particularly severe for anger ($p = 0.030$), happiness ($p = 0.034$), neutrality ($p = 0.016$), and surprise ($p = 0.016$), where the differences reached statistical significance.

A more in-depth analysis indicated that 21 participants with stroke showed accuracy comparable to the healthy subjects, while the remaining 25 participants had a relatively poor performance (**Table 2**). Differences in the overall accuracy of this latter group and the healthy controls reached statistical significance ($p < 0.001$); however, no differences in cognitive ability that involved visual perceptive skills were detected, except in part B of the color trail test. When analyzing performance by emotion, the individuals with stroke and poor performance showed significantly decreased accuracy in comparison to the healthy subjects at identifying anger ($p < 0.001$), happiness ($p = 0.006$), neutrality ($p < 0.001$), sadness ($p = 0.048$), and surprise ($p = 0.002$) (**Figure 1**).

Visual Behavior

No significant differences emerged when comparing the visual behavior of the individuals with stroke as a whole and with the healthy subjects; however, the individuals with stroke showed a tendency to spend less time ($p = 0.073$) and perform fewer fixations ($p = 0.056$) on the eyes in comparison to the healthy

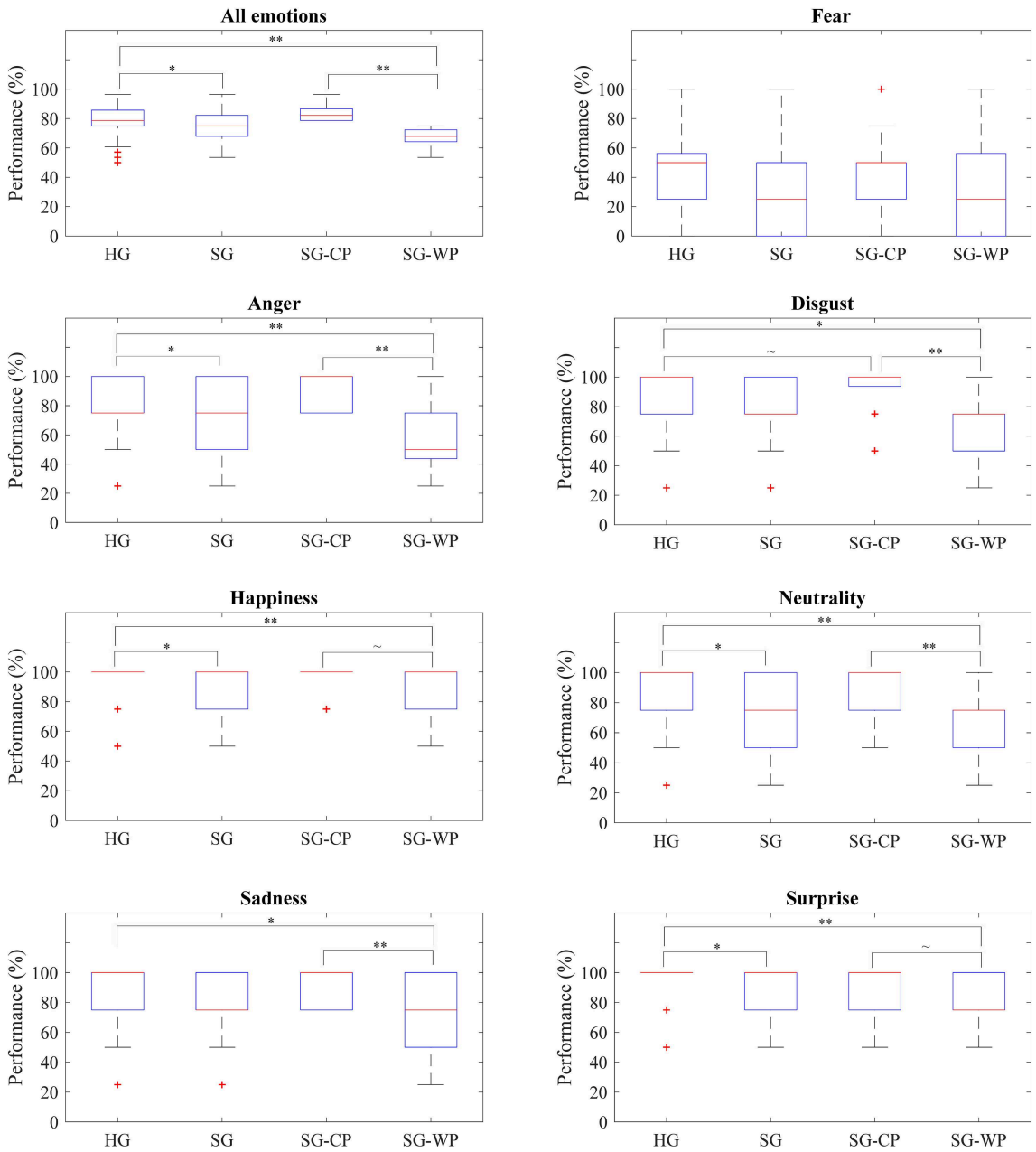

FIGURE 1 | Accuracy of each group of participants by emotion. Percentage of correct answers obtained by all groups of participants in all emotions and in each emotion, separately. HG, Healthy participants; SG, Participants with stroke; SG-CP, Participants with stroke with comparable performance to healthy participants; SG-WP, Participants with stroke with worse performance than healthy participants. $^{**}p < 0.01$, $^{*}p < 0.05$, $\sim p < 0.1$.

subjects. While the healthy subjects focused their attention on the eyes, nose, and mouth, in that order, the individuals with stroke mostly focused on the nose rather than the eyes. These differences were consistent for all emotions, and were statistically significant for fear ($p = 0.039$) and surprise ($p = 0.019$) (**Figures 2**, **3**).

No differences in visual behavior were detected between the healthy controls and the participants post-stroke with comparable performance, either when considering all emotions or when analyzing each emotion separately (**Figures 2**, **3**). In contrast, when compared to the healthy controls, individuals post-stroke with poorer performance showed a tendency toward significance in time spent on the eyes ($p = 0.059$) and fixations made on the eyes ($p = 0.076$), both variables having lower values than those of the healthy group. The separate analysis of each emotion showed significant differences between these groups in terms of time spent on the eyes for happiness ($p = 0.040$) and surprise ($p = 0.008$), and in the number of fixations for surprise

TABLE 2 | Characteristics of individuals with stroke grouped according to their performance.

	Individuals post-stroke with comparable performance	Individuals post-stroke with worse performance	Significance		
			HG vs. SG-CP	HG vs. SG-WP	SG-CP vs. SG-WP
Sex (*n*, %)			$p = 0.520$	$p = 0.242$	$p = 0.236$
Women	13 (61.9%)	10 (40.0%)			
Men	8 (38.1%)	15 (60.0%)			
Age (years)	48.0 (37–58)	55 (46–60)	$p = 0.706$	$p = 0.098$	$p = 0.114$
Etiology (*n*, %)			–	–	$p = 0.864$
Ischemic	9 (42.9%)[a]	9 (36.0%)[a]			
TACI	3 (33.3%)[b]	5 (55.6%)[b]			
PACI	2 (22.2%)[b]	3 (33.3%)[b]			
LACI	4 (44.4%)[b]	1 (11.1%)[b]			
Hemorrhagic	12 (57.1%)[a]	16 (64.0%)[a]			
Localization of the injury (*n*, %)			–	–	$p = 0.410$
Right anterior circulation	5 (23.8%)	15 (60.0%)			
Left anterior circulation	9 (42.9%)	8 (32.0%)			
Posterior	7 (33.3%)	2 (8.0%)			
Time since injury (days)	421.0 (230–641)	431.0 (214–1054)	–	–	$p = 0.700$
Visual perception and cognition					
Letter cancelation test (*n*)	10.0 (10–10)	10.0 (10–10)	–	–	$p = 0.801$
Wechsler Memory Scale IV					
Visual reproduction	8.0 (8–9)	8.0 (7–10)	–	–	$p = 0.851$
Rey–Osterrieth complex figure copy	33.0 (31–34)	31.0 (27–34)	–	–	$p = 0.134$
Color trail test					
Part A (s)	43.5 (35–59)	57.0 (38–75)	–	–	$p = 0.141$
Part B (s)	95.5 (78–121)	125 (92–165)	–	–	$p = 0.034$
Wechsler Adult Intelligence Scale IV					
Symbol search	23.5 (14–32)	18.0 (14–26)	–	–	$p = 0.281$
Matrix reasoning	16.0 (11–22)	18.0 (12–22)	–	–	$p = 0.972$

Demographic and clinical characteristics of healthy participants and individuals with a stroke. HG, healthy subjects. SG-CP, Individuals with stroke with comparable performance to healthy subjects. SG-WP, Individuals with stroke with worse performance than healthy subjects; TACI, Total anterior circulation infarcts; PACI, Partial anterior circulation infarcts; LACI, Lacunar circulation infarcts. Age, time since injury, and performance in the neuropsychological tests are expressed in terms of median and interquartile range.

[a] *Percentage of all participants with stroke.*

[b] *Percentage of participants with ischemic stroke.*

($p = 0.021$). Tendencies toward significance appeared in the time spent on the eyes for fear ($p = 0.053$) and in the number of fixations for fear ($p = 0.053$), happiness ($p = 0.055$), and sadness ($p = 0.092$) (**Figures 2**, **3**).

No differences were found between the visual behavior of any group for the mouth or nose.

Pupil Dilation

No significant differences were found in the variation in pupil dilation between the healthy subjects and individuals with stroke, or in general, or by emotion (**Figure 4**).

No significant differences emerged between the healthy subjects and the individuals with stroke with similar or poorer performance (**Figure 4**). However, individuals with stroke with poorer performance than the healthy subjects showed a tendency toward signification in fear ($p = 0.059$) and anger ($p = 0.098$) (**Figure 4**).

DISCUSSION

This study investigated the accuracy of responses to visual stimuli, the visual behavior, and pupil dilation in individuals with stroke while identifying emotional facial expressions in comparison to healthy subjects. The individuals with stroke showed a significantly relatively poor overall performance in comparison to the healthy subjects, which was also evident when analyzing each emotion separately. Although the different performances between the groups did not correspond to significantly different visual behaviors or pupillary activity, the individuals with stroke seemed to direct less attention toward the eyes and exhibited diminished pupil response. Importantly, when considering those individuals with stroke with impaired performance, these differences were significant for specific emotions. In contrast, the post-stroke individuals with comparable performance to the control group did not show

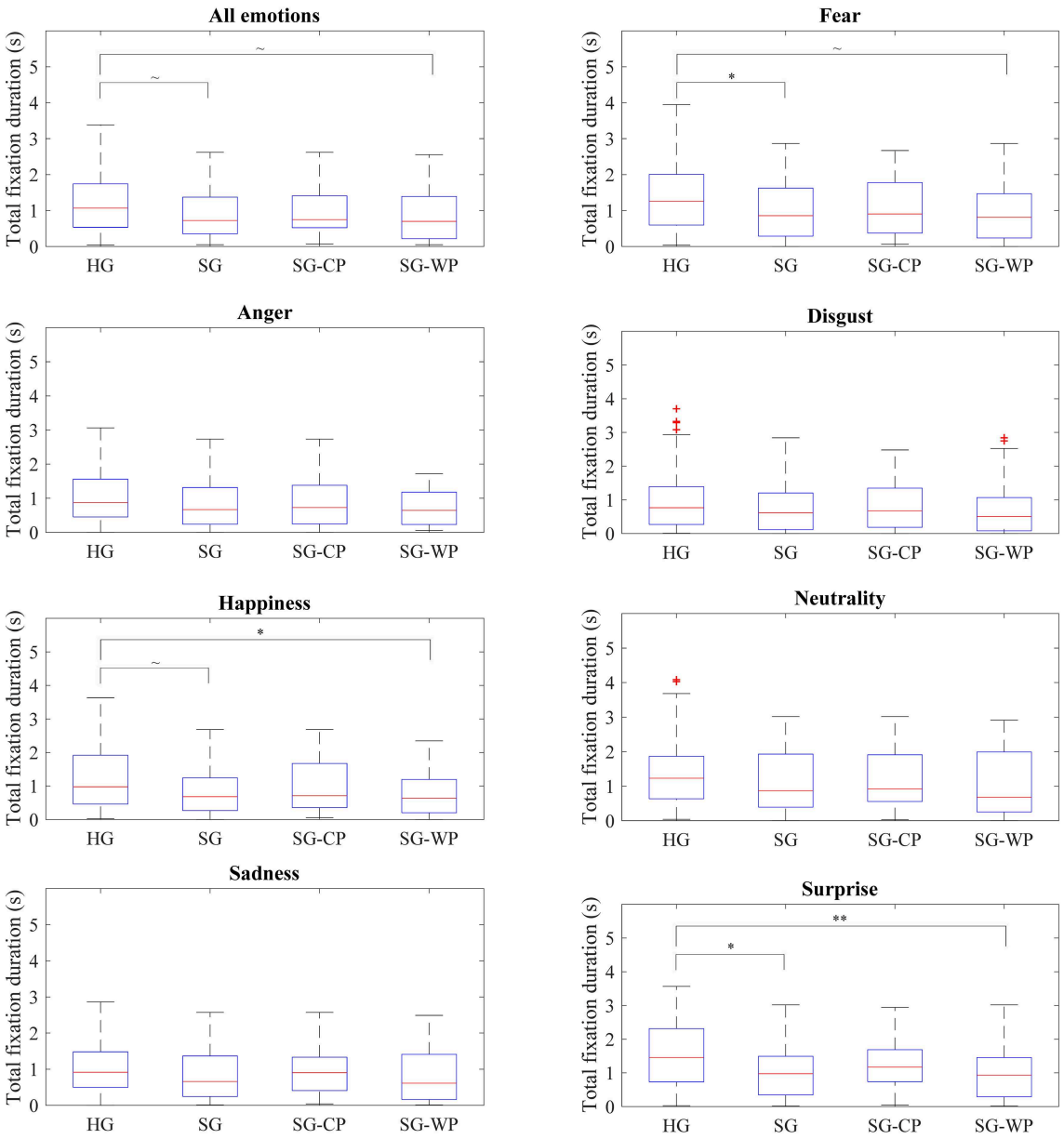

FIGURE 2 | Total fixation duration on the eyes of each group of participants by emotion. Total fixation duration on the eyes showed by all groups of participants in all emotions and in each emotion, separately. HG, Healthy participants; SG, Participants with stroke; SG-CP, Participants with stroke with comparable performance to healthy participants; SG-WP, Participants with stroke with worse performance than healthy participants. $^{**}p < 0.01$, $^{*}p < 0.05$, $\sim p < 0.1$.

any differences in their visual behavior or pupillary response from those of the healthy subjects. No relevant differences were found between the participants post-stroke with different performance in terms of any demographic or clinical variable, which supports the idea that an impaired ability to identify emotional facial expressions could be partially caused by altered visual behavior.

The ability of the healthy subjects in our study to identify facial expressions of emotion is similar to that reported in previous works, evidencing the greatest accuracy in identifying happiness and surprise, with opposite results in identifying fear (12, 15, 16). Their accuracy was, however, slightly inferior in all emotions in comparison to other reports (12, 15, 16). This effect was especially evident for fear, which had the lowest accuracy values. This might be explained by the fact that the healthy participants in our study, whose ages matched those of the individuals who had had brain injury, were significantly older than the participants in other studies, who were mostly recruited from the student bodies of universities and were, therefore, mostly in their 20s (12, 15, 16). As reported in previous

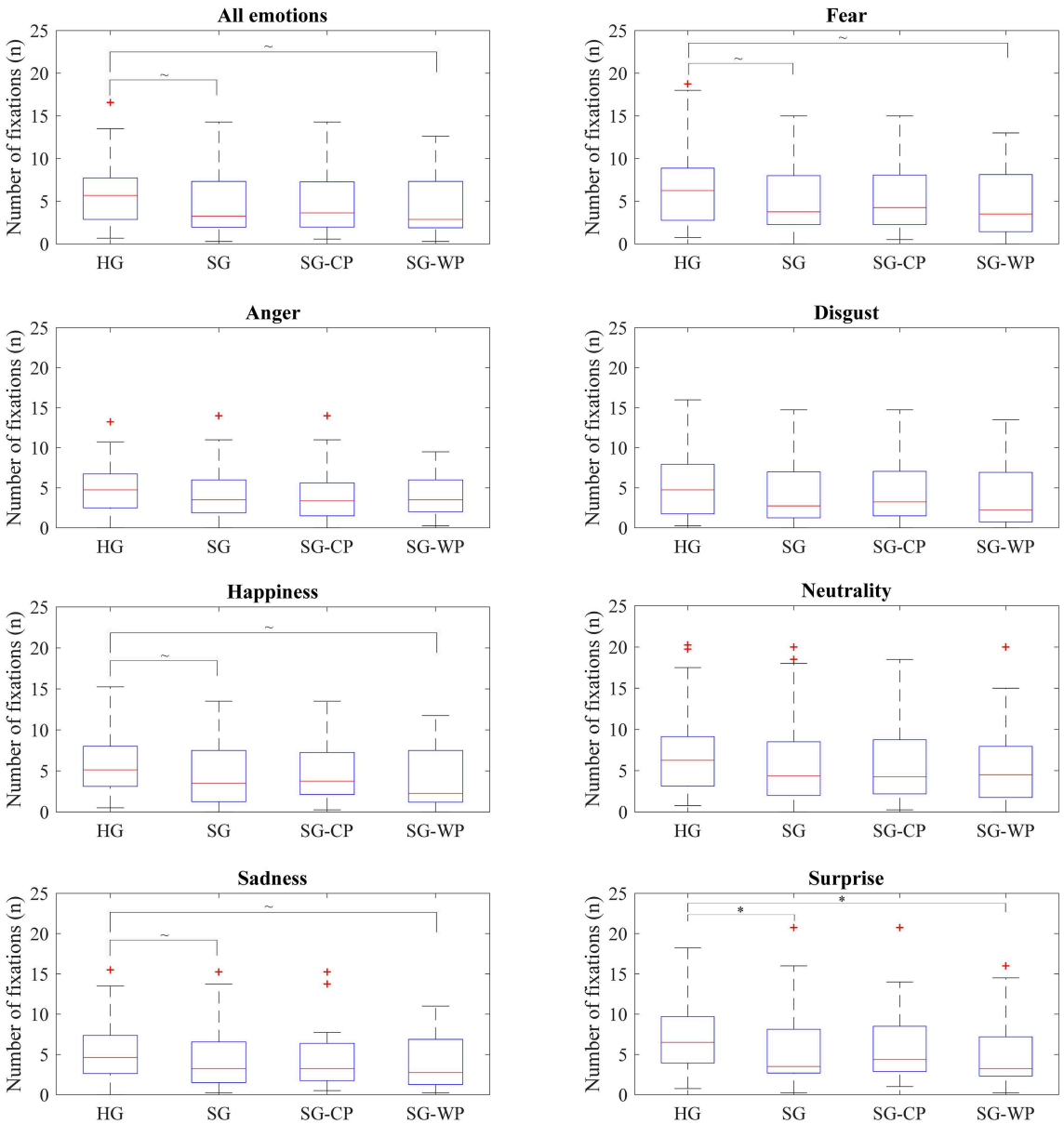

FIGURE 3 | Number of fixations on the eyes of each group of participants by emotion. Number of fixations on the eyes showed by all groups of participants in all emotions and in each emotion, separately. HG, Healthy group; SG, Stroke group; SG-CP, Stroke group with comparable performance; SG-WP, Stroke group with worse performance. *$p < 0.05$, ~$p < 0.1$.

studies, poorer performance at identifying emotional expressions is expected in older age (64, 65). In addition, although the images used in our study were extracted from the same database used in other studies (12, 15, 16), and the images were randomly selected, the emotions shown in the images may have been more difficult to recognize than in the images used in other studies. The visual behavior of the healthy participants was also consistent with existing reports, showing that eyes, noses, and mouths are the most relevant facial structures used in identifying facial expressions (12–15, 59). The hierarchical distribution of attention to the eyes, followed by the nose and the mouth, is also supported in most of the existing literature (11, 15, 16). In this study, the eyes were especially relevant when identifying surprise and fear, but seemed to draw less attention for disgust, which is consistent with a previous study (15). Nonetheless, it is important to highlight that there is no fixed or common pattern of visual behavior while identifying different emotions, as equally evidenced by our study and in previous reports (12, 15, 16). Additionally, our results must be taken into account considering that assessing accuracy by a simple count of the

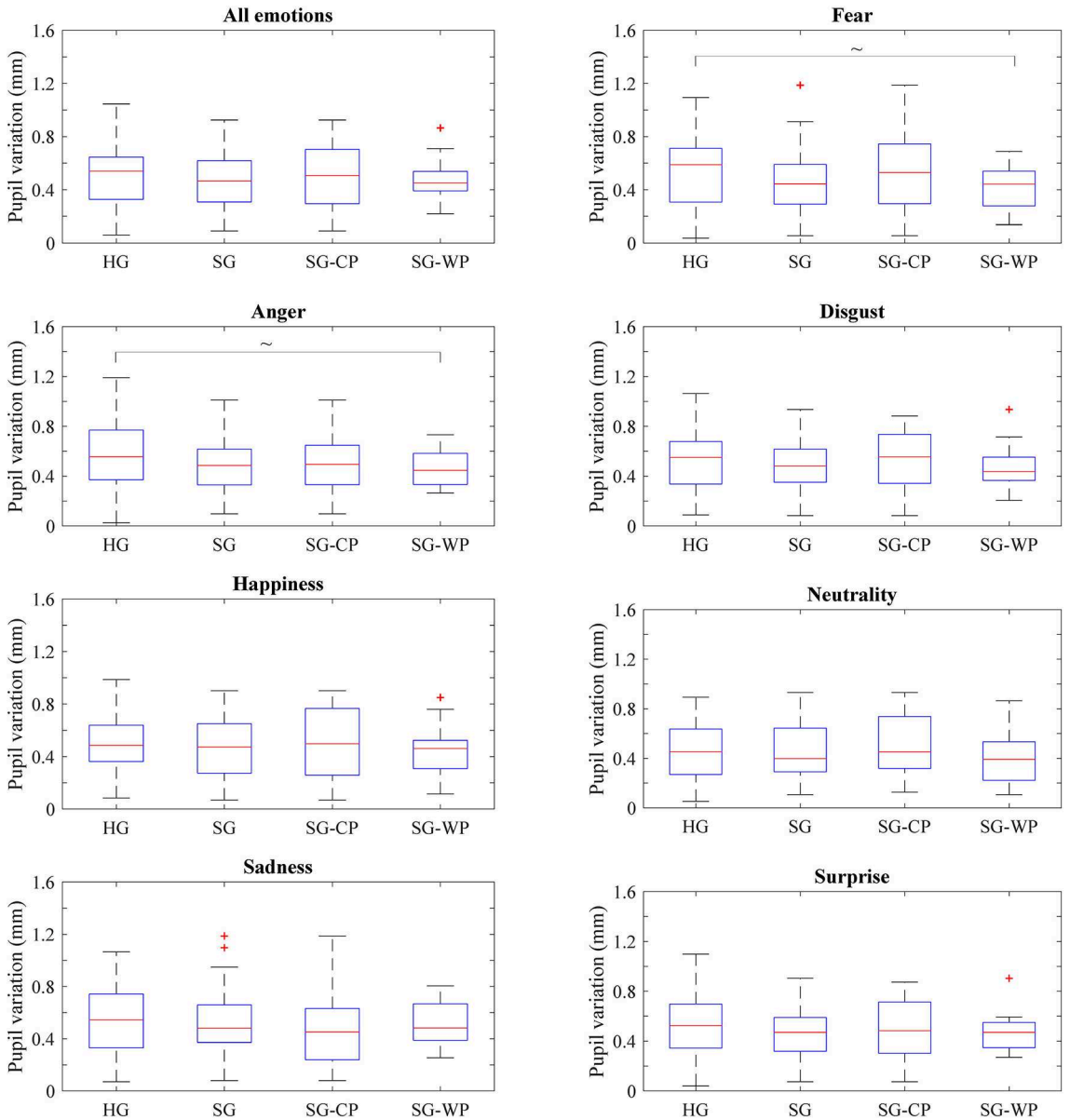

FIGURE 4 | Pupil dilation variation of each group of participants by emotion. Variation of the pupil size showed by all groups of participants in all emotions and in each emotion, separately. HG, Healthy group; SG, Stroke group; SG-CP, Stroke group with comparable performance; SG-WP, Stroke group with worse performance. $\sim p < 0.1$.

correct identifications without regard for false alarms or bias in the use of response categories, although it is the most common approach to analyze this behavior (8, 11, 12, 15, 16), could be misleading (66).

The variation in pupil dilation in our study was greater than that reported in previous studies (24, 60, 67). This dissimilarity may have derived from the use of different images, which, despite having been normalized, might have promoted different levels of arousal, consequently modulating the pupil response in a different way. Our results are, however, supported by a previous study, which reported the lowest variation in pupil dilation for expressions of happiness and neutrality, and the highest variation for fear (60). Despite this, it should be taken into consideration that variations in pupil dilation are triggered by different mechanisms, from simple autonomous processes, such as pupillary light reflex (18, 19), to high executive functioning (22, 27), so a definitive identification of the source of the variation is not possible using this technology. In addition, although the methodology of our study has been repeatedly used in previous investigations (25, 57, 60), it is important to

consider that the use of a black screen as a baseline may have negatively contributed to the identification of the source of the pupil variation.

Individuals with stroke showed impaired performance at identifying facial expressions of emotion, in line with previous studies (34, 43–45). Interestingly, these studies grouped the emotions by their attributes, reporting that individuals post-stroke exhibited better performance at identifying positively attributed emotions over negatively attributed emotions (43–45). This effect is also supported by our results, which showed the greatest accuracy for happiness and surprise, and the worst performance for fear. Nevertheless, the differences between the healthy participants and the individuals with stroke were not significant for all emotions, in contrast to what was reported in a previous study (43). The use of different images might explain these dissimilarities. Some emotions in our study might have been particularly difficult to interpret, affecting both groups in a similar way. The decreased attention toward the eyes exhibited by the individuals post-stroke in comparison to the healthy subjects is suggestive of an altered perception of visual information, which could partially explain their impaired ability to identify the facial expression of emotions. This hypothesis is supported by the differences in visual behavior for happiness and surprise, which represented a huge challenge to this group of participants. In contrast, differences in the accuracy of identifying anger and neutrality were not associated with differences in visual behavior when observing these emotions. The inconsistency in these results might reflect the complexity of the perceptual and cognitive processes underlying the decoding of facial expressions (3, 30). Although not statistically significant, individuals post-stroke showed a slightly diminished pupillary response compared to the healthy subjects, which, if endorsed in further studies, might reflect diminished emotional arousal, confirming previous reports (18, 23, 24). It is important to highlight, however, that pupil dilation is also driven by the co-activation of multiple brain areas (19, 68), which might be affected by a cerebrovascular accident.

In general, a comparison of the visual behavior and pupillary activity between healthy subjects and individuals with stroke only showed a decreased attention to the eyes, but this did not reach statistical significance. Although these results might support a degree of comparability between both groups, a separate analysis of the individuals with stroke, according to their performance, exposed significant differences. Differences between individuals with stroke with impaired performance and healthy subjects were stronger and significant for happiness, surprise, and fear. Pupil dilation was also lower and showed a tendency to significance for fear and anger. In contrast, participants with comparable performance showed similar visual behaviors and pupillary responses. The differences detected in groups with different performances, but an absence of any other clinical or demographic dissimilarities, suggest that altered visual behavior could be a contributing factor to impaired performance, rather than the neurological condition itself. Altered visual behavior, together with impaired emotional processing, which has been repeatedly reported after stroke (34, 43), could explain the accuracy of these individuals in identifying emotional facial expressions.

CONCLUSIONS

This study corroborated the negative effect of a cerebrovascular accident on the ability to identify facial expressions of emotion, which was also supported by analyzing the emotions separately. Our results showed that individuals with stroke looked for a shorter time and fewer times at the eyes than did healthy subjects, but without significantly differing from the pattern of observation of the healthy subjects. These differences were, however, accentuated when analyzing individuals with stroke according to their performance. While no differences were detected between the healthy subjects and the individuals post-stroke with comparable performance, this latter group showed increased and significant differences in different measures compared to healthy subjects, suggesting that altered visual behavior might be associated with, and be a contributing factor to, difficulties in identifying the facial expression of emotions after stroke. No significant differences were found in pupil dilation between healthy controls and individuals with stroke.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available as they contain confidential data.

ETHICS STATEMENT

Ethical approval for the study was granted by the Institutional Review Board of Vithas Hospital Valencia al Mar. All participants provided written informed consent before taking part in the study.

AUTHOR CONTRIBUTIONS

RL designed the study. BM, JF, and RL defined the clinical aspects regarding individuals with stroke, and BM assessed their condition. AM conducted the experimental sessions and analyzed the data. All the authors discussed the results of the experiment.

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REVIEW
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The Psychosocial Impact of Neurobehavioral Disability

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Neurobehavioral disability (NBD) comprises elements of executive and attentional dysfunction, poor insight, problems of awareness and social judgement, labile mood, altered emotional expression, and poor impulse control, any or all of which can have a serious impact upon a person's decision-making and capacity for social independence. The aim of this narrative review is to explore some of the more intrusive forms of NBD that act as obstacles to psychosocial outcome to act as a frame of reference for developing effective rehabilitation interventions. Special consideration is given to the psychosocial impact of three core forms of NBD: a failure of social cognition, aggressive behavior, and problems of drive/motivation. Consideration is also given to the developmental implications of sustaining a brain injury in childhood or adolescence, including its impact on maturational and social development and subsequent effects on long-term psychosocial behavior.

Keywords: neurobehavioral disability, social cognition, empathy, apathy, aggression, brain injury, psychosocial outcome

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INTRODUCTION

Neurobehavioral disability (NBD) is often considered a legacy of traumatic brain injury (TBI) but can follow any kind of brain injury, usually when the frontal system of the brain is compromised in some way. NBD is the product of an interaction between damaged neural systems, neurocognitive impairment, and environmental factors, further influenced by pre-morbid personality traits, post-injury learning, and a variety of environmental influences (1–3). It can take many forms, some of which involve a lack of social cognition (often involving problems of emotion-recognition and expression), or a lack of inhibitory control (such as labile mood, impulsivity, low tolerance, irritability, and poor temper control), while other forms present as diminished patterns of behavior (characterized by a lack of arousal-drive-motivation). When brain injury occurs during childhood or adolescence many forms of NBD can be more subtle, yet have a pervasive influence on maturational and social development. It is also the case that many aspects of NBD are not apparent in the early recovery stages after brain injury, only becoming evident when the injured person leaves a hospital or rehabilitation setting (both of which are highly structured environments) and have to begin to organize their lives, make decisions, re-establish relationships, and settle back into a constructive routine conducive to community independence.

NBD can act as a major obstacle to psychosocial recovery by undermining a person's capacity for independent social behavior and employment opportunities. Alterations to behavior and personality are long-lasting and enduring. They act as a significant barrier to making and sustaining relationships [e.g., (4)] and can impose a serious level of stress upon families

who often struggle to adapt to life with a relative who exhibits altered patterns of behavior (5–9). As time passes, relatives start to experience an increasing sense of "burden" (10), often because they are unaware of the neurobehavioral implications of brain injury and are unprepared for the emotional demands of the caregiving role (11, 12). Relatives experience a lack of control in their life planning (since they cannot schedule their activities) and uncertainty regarding their future because of ambiguity regarding their caregiving role (13–17).

Therefore, in order to provide an effective post-acute rehabilitation structure to maximize psychosocial recovery, knowledge of the nature and potential impact of NBD is vital in order to set meaningful rehabilitation goals, understand the probable time needed to achieve such goals, and indeed, whether the goals are realistic, considering a person's type or degree of disability. This review is not a systematic review about the topic, but a narrative overview that aims to raise awareness of some of the more intrusive forms of NBD and their potential psychosocial impact in order to provide a perspective for an effective rehabilitation framework.

A FAILURE OF SOCIAL COGNITION

Social cognition refers to the ability to attend to, recognize, interpret, and respond appropriately and flexibly to social cues that guide social behavior. Hence it is a broad construct in which different components can be distinguished. McDonald (18) made a distinction between *"hot processes,"* including emotion perception and the ability to empathize, and *"cold processes,"* which reflect the ability to infer the beliefs, feelings, and intentions of others (e.g., Theory of Mind—ToM) in order to see their point of view (cognitive empathy) and what they mean when communicating (pragmatic inference). Thus, social cognition consists of different and dissociable, but interrelated processes (19).

Social cognition appears to be underpinned by a frontal subcortical network, including orbital and ventromedial regions (20, 21), the cingulate cortex and striatum, insula, and amygdala (22, 23); structures particularly vulnerable to traumatic brain injury (TBI) either due to focal, multifocal or diffuse axonal injury (24–26). Consequently, it is perhaps unsurprising that impairments in social cognition have been frequently observed after TBI, including deficits of emotional perception and recognition [e.g., (27, 28)] and ToM (29, 30), which often culminate in a lack of empathy (31).

Diminished Empathy

Empathy involves three primary components: *cognitive empathy*—the ability to appreciate and understand how and why a person exhibits an emotional state; *emotional empathy*—the capacity to vicariously experience and share the perceived emotional experiences of others (31); and *compassionate empathy*; an appraisal mechanism that keeps track of feelings experienced by oneself and others, allowing one to decide whether it's appropriate to respond compassionately (32). Therefore, empathy requires the ability to share (emotional empathy) or understand (cognitive empathy) another's emotional state and then feel concerned about that person's welfare (compassionate empathy).

In a sample of 89 individuals with TBI, Wood and Williams (33) found that 60.7 per cent reported low levels of emotional empathy, compared with only 31 per cent of a demographically matched healthy control group. Interestingly, they found no significant relationships between emotional empathy and cognitive abilities (i.e., cognitive flexibility, executive function, verbal ability), suggesting that emotional empathy may operate in a manner that is relatively independent of cognitive ability *per se*. They also found no obvious relationship between emotional empathy and measures of affective distress. Finally, evidence suggests that emotional empathy is unrelated to the severity of TBI (31, 33), implying that even relatively minor head injury (presumably in vulnerable individuals) has potential to disrupt the capacity to empathize.

The Role of Alexithymia

One such vulnerability factor is alexithymia, a multifaceted construct comprising: (a) difficulty identifying and describing emotions; (b) a concrete communication style; (c) an externally oriented style of thinking, and (d) limited imaginal capacity (34). Clinically, individuals exhibiting alexithymia demonstrate little knowledge about their own feelings and, in most instances, are unable to link them with memories, fantasies, higher level affects, or specific situations (35). It is a normally distributed personality trait present in 7-12% of the population (36, 37) and, whilst not intrinsically pathological, it has been conceptualized as one of several personality risk factors for a variety of medical and psychiatric disorders involving problems of affect regulation [For a review, see (38)].

Recent studies have revealed a much higher incidence (57.4–72.3 per cent) of alexithymia after TBI (31, 39–41), with the terms "organic" and "acquired" alexithymia subsequently adopted to descriptively distinguish constitutional deficits associated with a developmental history of affective and personality disorders, from an acquired disorder following TBI. Further, Williams and Wood (31) found an inverse relationship between alexithymia and emotional empathy in 64 cases with TBI and 64 demographically matched healthy controls, suggesting that the presence of alexithymia may render an individual unable to vicariously experience the emotions of others (emotional empathy).

The Impact on Social Behavior and Relationships

Behaviorally, a lack of empathy after TBI is often observed via a lack of social tact and social discretion, selfish and socially immature behavior (17, 42), an egocentric, self-centered attitude that is insensitive to, or neglectful of, the needs of others (3, 43), and a lack of emotional affection and relational connection with loved ones (44, 45). Unsurprisingly, a lack of empathy after TBI can therefore contribute to the fragility of close personal relationships when a partner, who was previously loving and affectionate, remains physically present but psychologically absent, emotionally withdrawn, and aloof after their injury. Indeed, it is not uncommon for spouses of individuals with TBI to

describe their partners as a *"complete stranger"* since their injury, with their relationship no longer feeling like a marriage (8, 44, 46).

Close personal relationships following TBI therefore appear to be particularly vulnerable to strain and breakdown, with the rate of divorce typically higher than general population estimates of 22–42 per cent (47). For example, Wood and Yurdakul (48) found that 49 per cent of their UK sample of 131 couples had divorced or separated during the 5–8 year period following injury, with the rate of divorce increasing over the passage of time. This was assumed to indicate partners progressively losing hope that their loved one will recover and a realization that the permanence of the condition can no longer be denied. However, more recent examination of marital stability after TBI presents a stark contrast to earlier reports (49, 50). In a sample of 120 patients with mild to severe injuries, Kruetzer et al. reported a similar rate of divorce (17 per cent) as found by Wood and Yurdakul, but a much lower separation rate (8 per cent). This can be explained in part by a lack of consistency in assessment procedures, partly by the large socio-cultural differences between study samples, and partly on the basis of time since injury. For instance, Wood and Yurdakul followed-up cases 5–8 years post injury, concluding that 5 years post injury was a watershed for couples deciding to separate. By contrast, the Kreutzer study followed-up cases 2.5–7 years post-injury, potentially including a number of cases who had not yet reached the watershed point.

Despite uncertainty concerning divorce and separation rates following TBI, relationship stability and quality is generally reported to be low (4, 40). Peters et al. (51) found that partners of individuals with severe TBI reported significantly lower levels of marital satisfaction, cohesion, adjustment, and affectional expression compared to partners whose spouse had sustained a spinal cord injury. Similarly, Gosling and Oddy (52) reported significantly poorer marital satisfaction, plus a lack of expressed affection and emotional responsiveness in couples 1–7 year's post-TBI. They also noted that the non-injured partner was often more dissatisfied with their relationship than their injured spouse, a finding also supported by Williams and Wood (40). This highlights how many individuals with TBI lack awareness and insight into the impact of their injury on their significant others (53, 54).

The high rates of relationship breakdown and dissatisfaction following TBI described above have been linked to a wide range of factors, including changes in behavior, personality and neuropsychological function (4, 55), sociodemographic factors (56, 57), specific relationship factors [i.e., length of relationship; (48, 58)], and injury-related variables, such as severity of injury or time since injury (49). However, for many partners and spouses of individuals with TBI, the most challenging and destructive relationship behaviors following injury include a loss of emotional responsivity, a lack of mutual emotional support and companionship, and a loss or reduction in overt acts of affection. For example, relationships can suffer when individuals with TBI lack understanding of other people's social behavior and intentions (30), appearing insensitive or indifferent to the emotional needs of loved ones as a result.

Similarly, close personal relationships can be further compromised when partners or spouses report a sense of rejection, emotional isolation and detachment. This can occur if the relative to whom they provide care and support lacks empathy and seems emotionally cold and distant toward them, in contrast to their pre-accident behavior (33). This may create a feeling on the part of the relative that the support they give is not valued, a perception thought to be a significant contributor to both an objective and subjective sense of burnout. Sundin et al. (59) have also found that perceptions of poor appreciation from others involved in one's work or care role predicted emotional exhaustion, feelings of depersonalization, and a sense of poor personal accomplishment. In addition, Wells et al. (60) found that a lack of empathy on the part of the survivor uniquely contributed to a reduction in perceived life satisfaction in their sample of caregivers, of whom the majority were spouses.

How a spouse reacts to their partner's lack of empathy, and other stressors attached to their caregiver role [see (61)], will invariably depend on how they themselves experience and/or reflect on their own emotions. For instance, the presence of alexithymia has been positively correlated with higher levels of burnout and emotional exhaustion, as well as negatively correlated with feelings of personal achievement in occupational and professional samples [e.g., (62, 63)]. Similarly, in a sample of relatives of individuals who had sustained a TBI, Katsifaraki and Wood (64) found higher levels of emotional exhaustion and depression, as well as reduced levels of self-accomplishment in a sub-group of relatives reporting alexithymia, than a sub-group without alexithymia. More broadly, Mattila et al. (65) also found that difficulty identifying feelings (a core component of alexithymia), was associated with occupational burnout after controlling for depression and various sociodemographic factors. They also noted that alexithymic individuals were prone to burnout because of the adoption of dysfunctional coping mechanisms in order to deal with stressors, an observation also made by Demerouti et al. (66) and Parker et al. (67), as well as Wood and Doughty (68) in the context of TBI specifically.

Risks of Social Isolation

In addition to close personal relationships, poor emotional perception, leading to a lack of emotional expression and an empathic response, may also help to explain why a high proportion of individuals with TBI experience deficiencies in social-interpersonal behavior that lead to a decline in social and leisure activities, diminishing social networks, poor community integration, and high levels of social isolation and loneliness (69–73). For instance, May et al. (74) found that poor emotion recognition abilities post-injury were associated with poor social functioning and fewer independent social activities outside of the home (i.e., community integration). An association has also been made between empathy and interpersonal behaviors that can directly, or indirectly, undermine social competence. For instance, Saxton et al. (75) found that perspective taking deficits (a critical component of empathy) were significantly related to both self-reported interpersonal (i.e., difficultly getting along with other people; getting into arguments easily) and communication problems, such as failing to listen carefully and respond normally

when talking to others. From this perspective, it is likely that difficulty understanding another person's point of view restricts an individual's ability to effectively interact with others, such as exhibiting poor listening skills, misinterpreting the behavior of others and responding inappropriately (i.e., temper outbursts, emotional lability), failure to adjust behavior in accordance with social rules and demands, or communicating information that is irrelevant, insensitive, or redundant to the social situation. Consequently, such interpersonal and communication patterns are likely to alienate others, exerting an adverse impact on the size or quality of a person's wider social network.

In such circumstances individuals have fewer opportunities to observe and practice appropriate social-interpersonal communication, helping to explain the relative temporal stability and persistence [i.e., (76)] of such social-interpersonal difficulties over a long period of time post-injury. If the availability of meaningful social feedback is reduced it may add to lost opportunities to learn from experience, potentially leading to further social ineffectiveness and isolation, difficulty establishing new social contacts and friends, heightened feelings of failure, frustration and low self-esteem, and increased dependence on family members for social interaction and access to community and recreational activities. Crucially, this increased reliance on family members places additional strain on what are already fragile relationships, exacerbating the risk of relationship failure (4, 40) as well as caregiver stress, burn-out and psychological distress (61, 77). Therefore, in situations where close personal relationships dissolve after brain injury, the individual may not only have to come to terms with the loss of a partner, but also their primary, and potentially last, remaining source of social and emotional support.

Social isolation and lost social supports have additionally been linked to the adoption of maladaptive coping strategies that may further undermine recovery after TBI. For example, those who are socially isolated after TBI are more vulnerable to alcohol and drug dependency because of both their perceived direct mood-altering effects and the desire to compensate for a lack of socially meaningful and fulfilling contact with others [see (78, 79)]. This is particularly problematic as the behavioral and emotional effects of such substances and TBI are considered synergistic, leading to further negative impacts on an individual's social-interpersonal and psychosocial recovery.

AGGRESSIVE BEHAVIOR

Aggression is arguably the most overt and debilitating feature of NBD (80) because of the serious impact it has on the survivor, their family and community. When aggressive behavior occurs in the context of rehabilitation, it can also prevent survivors achieving their full recovery potential (81), with some excluded from rehabilitation altogether. When this happens, individuals with brain injury gravitate to placements ill-equipped to meet their needs, including forensic and secure mental health services (82).

However, there is considerable variability regarding its prevalence. For example, in a review of the literature, Tateno et al. (83) found that rates of aggressive behavior amongst samples of TBI survivors varied from 11– 96 per cent. This extreme variability is partly attributable to the non-homogeneous nature of ABI, the lack of a standardized definition of what constitutes aggression, and methodological issues regarding how and when, or in what context, it is measured.

Measuring Aggressive Behavior

Our understanding of aggression and its impact on psychosocial outcomes after brain injury can be improved by using standardized measures which incorporate clear, objective operational definitions of behaviors, such as those included in observational recording measures, like the "Overt Aggression Scale—Modified for Neurorehabilitation" [OAS-MNR: (84)] and the "Overt Behavior Scale" [OBS: (85)], both of which share the same operational definitions of different types and severity of aggression. When using such measures, prevalence rates between 40 and 90 per cent have typically been reported, with verbal aggression accounting for the greatest proportion. For example, using the OBS, Kelly et al. (86) investigated challenging behavior profiles of people who had suffered brain injury in the community, reporting that 85 per cent had engaged in verbal aggression, 41.1 per cent physical assaults on other people, and 35.3 per cent physical aggression toward objects. Some of the variability in prevalence reflects how long after injury data was captured, as the tendency is for aggression to increase over time. In addition, the impact of context on behavior is also evident from studies reporting on the prevalence and impact of aggression on psychosocial function in residential and hospital settings, which might typically be expected to manage those TBI survivors with the most challenging behavior. For example, Alderman et al. (87) described 5,548 aggressive events, including 729 physical assaults on other people, exhibited by 108 ABI survivors engaged in neurobehavioral rehabilitation over a 14 day period.

Psychosocial Impact

However, aggressive behavior, like many other features of NBD can have complex origins so predicting its psychosocial impact is not straightforward. Accounts typically discriminate between aggressive behavior which has a predominantly neurological basis from behavior that is primarily attributable to neurocognitive impairment (88). Consequently, it is important to understand how these two forms impact on psychosocial function in order to devise effective rehabilitation interventions.

Briefly, and regarding neurological causes, lesions to the orbitofrontal cortex and its connections are especially implicated in aggression. Damage to the orbito-temporal-limbic feedback loop disrupts the inhibitory function of the cortex over the amygdala, depriving the cognitive functions of any ability to suppress instinctive emotional reactions (89). Aggressive behavior with this etiology is provoked by clear antecedents. A further category of neurologically mediated aggression is the episodic dyscontrol syndrome (EDS), one of the post-traumatic temporo-limbic disorders. EDS aggression tends to

be brief, and 'out of character', often without obvious triggers. If there is some form of trigger it is usually minor and the magnitude of the behavioral response is grossly out of proportion. Whilst those with EDS often express regret over their behavior (usually in contrast to those who exhibit impulsive aggression), the unexpected nature of the aggressive outburst can have an extremely adverse emotional impact upon families (3).

Regarding neurocognitive impairment, executive function disorders are especially implicated in aggression. Reduced ability to initiate or use preserved abilities, monitor performance and utilize feedback effectively to regulate behavior, results in lack of "error awareness," usually observed as disinhibition, impulsiveness and poor response to cues. This has a grossly negative impact on psychosocial function, incapacitating performance in social situations, reflected by low frustration tolerance and little ability to inhibit aggressive responses (88). This type of aggression is often underpinned by a form of procedural learning, especially when aggression serves an avoidance/escape function (90).

Irritability is similarly more evident amongst people with brain injury, especially TBI (91) and is strongly associated with overt aggression. Reports of incidence vary [for example, 29–69% in TBI, see (92)] and, as is also the case with aggression, some of this variance is attributable to lack of a standardized definition. However, most sources define irritability as involving an internal experience (becoming easily annoyed, upset) as well as overt expressions reflecting that experience (88). Irritability and aggression have been conceived as comprising opposite ends of a continuum; upsurges in irritability increase the likelihood of aggressive acts, with a variety of mediators underpinning movement along the continuum. For example, there is some evidence that severity of injury may act as one such mediator. Yang et al. (91) found a strong association between irritability and information processing ability amongst mild TBI survivors, which may be an important antecedent to aggressive acts described earlier regarding neurocognitive impairment and lack of error awareness. Conversely, they found no such association in survivors of moderate and severe TBI, concluding that irritability was a direct consequence of the brain lesions involved. As described above, this would be consistent with the association of aggressive behavior with lesions to the orbitofrontal cortex and its connections, and the subsequent deprivation of the cognitive functions in supressing emotional reactions.

Impact on Community Living

There is a negative association between increased levels of challenging behavior, including aggression, with decreased levels of functional ability, increased care needs and decreased participation in life roles amongst TBI survivors in the community (93). For example, aggression features frequently in qualitative studies capturing the perspective of family members, many of whom attribute much of the decline in psychosocial function to this behavior. Braine (94) found that relatives commonly identified increased aggression and memory disturbance as being responsible for a number of negative experiences, including emotional turmoil, social isolation and concern for the future. Fear of behavioral outbursts was of particular concern. Similarly, Tam et al. (95) interviewed caregivers of severe TBI survivors in the community, finding that verbal outbursts, amongst a broad range of other challenging behaviors, were frequently cited as a significant concern. Distress and caregiver burden was especially highlighted with the additional consequence of reduced community integration for TBI survivors.

Gould et al. (96) interviewed TBI survivors either living at home or in residential accommodation, their close others, and clinicians regarding the impact of challenging behavior, including aggression. Some differences were found. Verbal and physical aggression were characteristic of survivors in the community, who were also found to have awareness of these behaviors and their psychosocial impact. In residential settings there was a broader range of challenging behavior, including violence that was more severe than that exhibited in the family home. This group also tended to lack awareness regarding their behavior and its consequences. Verbal aggression took the form of shouting, swearing and threats of physical violence, often alongside acts of physical aggression. Frustration and loss of control were reported as underpinning much of this. By contrast, aggression displayed within the home setting was more often associated with socializing or in formal interactions with authority figures, including the police. Aggressive reactions reflected impairments in social cognition, whereas in residential settings, the main cause of aggression was being prompted to perform personal care tasks. Aggression and concern about the unpredictability of violence was also noted to be very distressing to relatives, along with fear of the consequences of this behavior (police involvement and incarceration). Factors that triggered aggression included: a) a lack of routine and consistency (especially in residential settings); b) mental health problems (especially depression and anxiety); c) increased awareness, and d) a lack of meaningful activity. In addition, aggression in residential settings potentially served a number of additional functions, including attracting attention, avoiding activities and regaining control.

Risk of Offender Behavior

Williams et al. (97) found that the tendency to react aggressively is associated with an increased risk of offender behavior and contact with forensic services, evidenced by the finding that individuals with TBI are overrepresented in UK prison populations (see later section on developmental implications). Associations between aggression and offending after TBI have also been reported in large scale Swedish population studies [e.g., (98)]. For example, Fazel et al. (99) demonstrated that violent crime was over-represented amongst people with TBI compared to the general population (8.8 vs. 2–3 per cent).

DISORDERS OF AROUSAL, DRIVE AND MOTIVATION

Motivation is essential to adaptive functioning and quality of life. Clinicians know that without motivation, individuals with TBI will fail to keep appointments, neglect their medications, become distant to friends and family, or fail to return to work. A lack of

motivation imposes constraints on physical rehabilitation and the development of coping skills. It can also be an important source of burden for families who care for individuals after TBI (12).

The terms *arousal, drive* and *motivation* represent a continuum of psychophysiological function which can be disrupted at different points and to different degrees depending on the location and severity of the brain injury. Arousal reflects a general awareness of sensory stimuli and preparedness to respond (100). It is considered as a general state without a specific target or stimulus, analogous to cortical tone, which fluctuates during wakefulness or sleep. Deficits in arousal concern the energizing (quantitative) aspects of purposeful behavior rather than the directional (qualitative) aspects. Consequently, arousal deficits are characterized by lethargy and drowsiness. Clinically the presentation may be confused with loss of drive and these terms are sometimes (incorrectly) used interchangeably.

The term "drive" has a more ambiguous meaning but should be considered to refer to lack of purpose to act in people who appear fully alert. Wood and Eames (101) describe drive as a basic physiological process, a property of the organism which provides the impetus for behavior. Whilst intrinsic to the individual, drive is also stimulated by the environment, different external cues activating drive to a variable extent. Drive-based disorders often underlie descriptive terms, such as anergia or adynamism. Psychic akinesia refers to a loss of spontaneous mental processing in the context of normal externally-triggered mental function. It has been termed auto-activation disorder (102) and indicates a form of higher-order deficit in the generation of ideas, more fundamental and separate from motivation, and occurs in the context of normal intelligence (103). Brown and Marsden (104) described abulia as a kind of psychic akinesia, noting that this condition is characterized by apathy but not low mood. Abulia consists of a symptom cluster which includes aspontaneity and slowness and rigidity of movement. However, there is less consensus amongst practitioners on whether it should be understood as a primary disorder of motivation or a disconnection between the desire to act and the ability to act on that intention (105).

The construct of motivation is considered by many to be at the highest level of purposeful behavior, usually defined as an incentive or reason for acting. Whereas arousal is a general physiological state, with drive representing the physiological basis for goal-directed behavior, motivation is a more complex psychological construct that encompasses diverse cognitive and affective factors. Diminished motivation is fundamental to Marin's (106) influential concept of apathy, which he characterized as an impairment in goal-directed thoughts and behaviors, a loss of interest, combined with indifference to planning or setting goals, plus a lack of effort to achieve simple goals set by others.

Disorders that reflect diminished motivation are also linked to executive dysfunction. For instance, the pursuit of goals requires the capacity to identify, evaluate and prioritize goals, but also the ability to ignore external distractions, suppress other internal drives and initiate purposeful behavior. A deficit in any of these processes can result in similar psychosocial consequences but careful analysis will yield more information about underlying difficulties. To assist clinical assessment, Oddy et al. (107) proposed a five-stage model incorporating physiological, motivational and executive components as a basis for conceptualizing and treating a wide range of motivational disorders after TBI.

Neural Basis of Drive and Motivation Disorders

Neurological disorders of arousal and drive are commonly associated with damage to brainstem and basal forebrain structures or cortico-subcortical networks involving the thalamus. The brainstem Ascending Reticular Activating System (ARAS) connects the thalamus, hypothalamus and basal forebrain, with the brainstem and forebrain providing important cholinergic inputs to thalamic nuclei. Central thalamic neurons are thought to be involved in supporting a distributed network which maintains neuronal activity through cortico-striatopallidal-thalamocortical circuits (108). These thalamic neurons are involved in responses to situational change, such as increased cognitive demand and stress. Damage to these circuits results in impairment of arousal regulation and forebrain activation underpinning goal-directed behavior.

The neural basis of motivation is less well-understood, with research largely focussing on apathy in the context of progressive neurological conditions. Such research indicates a complex relationship between psychological factors such as subjective value and outcome expectancies mediated by fronto-subcortical circuits linked to reward sensitivity and emotional state and ultimately dependant on effective motor networks. The role of mesolimbic dopamine for translating motivation into action has long been recognized and notions of dopamine depletion underlie many attempts to explain impairments of drive and motivation. Damage to the dopamine-rich ventromedial prefrontal cortex is linked to a range of deficits in sensitivity to reward, emotion-based learning and decision making. In addition, a wide range of subcortical structures including the anterior cingulate, hippocampus, insula, striatum and amygdala have been implicated in mediating stimulus-reward associations that drive purposeful behavior. Evidence for the role of specific brain structures in neurobehavioral disorders of diminished motivation and their psychosocial sequelae after traumatic brain injury has been reviewed recently by Worthington and Wood (12).

Psychosocial Impact of Drive and Motivation Disorders

Apathy and diminished motivation have been associated with a wide range of negative consequences, such as poor recovery and rehabilitation outcome (109, 110), loss of social autonomy (111, 112), loss of vocational opportunities, with obvious financial implications (113), risk of cognitive decline (114), caregiver distress (115), poor quality family life (115), and poor social reintegration (112).

Psychological Impact

In understanding the impact of diminished motivation on the individual with brain injury it is important to consider how this is defined and measured in order to take account of confounding variables such as depression. Most research concerns apathy. Estimates vary from 20 to 70 per cent (113, 116). For example, (117) found that apathy (mixed with depression) occurred in 60 per cent of their sample, whilst Andersson et al. (118) found that almost half of their TBI sample had significant degrees of apathy. Apathy often occurs alongside other problems such as depression, fatigue and dysthymia, leading to difficulty establishing whether apathy is a primary disorder reflecting neurological damage or part of a broader set of symptoms of an underlying psychological disorder. Marin (119) argued that apathy or diminished motivation as a disorder was not caused by emotional distress and it would be illogical to refer to someone as *suffering* from apathy. Levy et al. (120) argued that apathy or lack of motivation should not be assumed to reflect depression, with the latter being characterized by sadness, hopelessness and worthlessness. Similarly, Marin and Wilkosz (121) highlighted that depression, but not apathy, is characterized by dysphoria.

Psychologically, the impact of apathy on the individual is often very limited, reflecting the impact of emotional blunting with little impetus for change. People with apathy often express indifference to their situation; they may know what should be done, and they are aware of their failings, but do not exhibit the frustration or distress that usually accompanies such insights. Instead, it is their loved ones who express these reactions when faced with an apathetic relative.

Impact on Daily Living

Although not typically associated with personal psychological distress, disorders of drive and motivation can severely undermine the ability to care for oneself and function autonomously, increasing dependence, even in people with preserved intellect. This is often mistaken for wilful behavior, such as laziness or obstinacy, or a form of self-neglect related to depression, when it is really a lack of impetus for behavior. This was neatly summarized by Pachalska et al. (122) when distinguishing between the inability to complete a task due to poor decision making and errors, from those who "*fail in task performance because they never actually begin: rather than make wrong decisions they make no decision at all, even though in most cases these patients can describe in detail what needs to be done*" (p. 2)

Shallice et al.'s (123) description of their case DN is typical: "*He is untidy. Shaving, changing his clothes or undergarments, washing his hair and having his hair cut are only carried out when his wife tells him. He hardly ever spontaneously tackles any domestic chores . . . if his wife is out, he normally leaves the preparation of a meal to his 10 year-old son*" (pg. 730).

However, even when a person may lack the facility for acting spontaneously, they could still be stimulated into action by situational triggers. Someone may lack spontaneity and sit about aimlessly whenever left alone but will readily engage in activity if prompted, for example by a text message or telephone call. Sometimes the action is only triggered in the presence of another person to cajole or model the behavior, and is only maintained by the same level of assistance.

People who lack internal motivations may be especially susceptible to cues in their environment. Lhermitte et al. (124) described an environmental dependency syndrome in which he postulated that the person's decision to act was not one they made for themselves. He described several such cases, including a lady who was apathetic all day but who could prepare a meal perfectly once in the kitchen if asked to by her husband, "*mental inertia and apathy played a part in the sense that the patients were powerless in the face of influences from the outside world*" (pg. 342).

Luria et al. (125) similarly described a 'pathological inertia' linked to frontal lobe lesions, "*Clinicians are well aware of the fact that patients of this group cannot look after themselves; even if hungry they will not ask for food and will not, of their own accord, reach for it. Bread must be put into their hand or they must be given a spoon in order to trigger the act of eating*" (p. 237). Consequently, the support needs (and care burden) of people with diminished drive and motivation are often considerable in order to fulfil their potential for adaptive living which they are incapable of doing when left to their own devices.

Impact on Relationships

Most research on the impact of TBI on relationships does not address the effects of diminished drive and motivation in isolation but it is frequently cited as a key factor. In one early study, aspontaneity after brain injury was one of the most common complaints of relatives (126). Lack of spontaneity was also evident in the author's 10-15 year follow up in 18 of 35 cases (127). McKinlay et al. (7) reported that the most frequent complaints of relatives at three, six and 12 months post-injury were slowness, tiredness and irritability, all of which were reported in at least two-thirds of respondents at each stage of recovery. Rosenbaum and Najenson (45) reported that partners felt depressed and isolated, with depressed mood amongst wives correlated with reduction in the brain-injured partner sharing childcare and their own child-like dependency. Subsequently, in a series of structured interviews inertia was reported by 89 of 98 "collateral" informants (partners, caregivers, colleagues) as a significant problem (128). This suggests that lack of drive and motivation is a major factor disturbing equilibrium in a relationship.

Apathy is more commonly reported by relatives (129) and clinicians (118) than brain injured persons themselves (130) but is often misinterpreted. Efforts made to energize individuals who are apathetic can elicit an aggressive reaction (131). This adds significantly to the stress of living with a family member who exhibits diminished motivation, whilst their failure to partake in marital or family activities can leave the whole family feeling estranged. This was explored recently using the Apathy Inventory. Arnould et al. (129) measured apathy, care burden and psychosocial functioning in close relatives of 68 adults with severe TBI (30 parents, 27 spouses and 5 siblings). Results showed that aspects of apathy (emotional blunting, lack of interest, lack of initiative) were linked to relatives' subjective care burden whereas

poor psychosocial functioning was associated specifically with emotional blunting.

Impact on Employment

Disorders of drive and motivation have not been systematically studied as barriers to employment in their own right but clinicians are familiar with the problems they cause for vocational reintegration. In their early study of social recovery of 54 severe closed head injured adults, Oddy and Humphrey (132) reported that all but six had returned to work within 2 years, with physical disability considered a greater impediment than personality changes. This is not surprising if one considers that physical deficits are usually more apparent and can have more obvious constraints on ability to work. Getting back to work is not the same as being able to maintain employment however and it is likely that ultimately, job-limiting changes in temperament take time to emerge. These authors also point out that although ostensibly people were back in the same job employers reported subtle alterations in their expectations. This is a key point: the work environment may be sufficiently structured to allow people with some residual motivation to function adequately, whilst supportive employers may be able to adjust the work role sufficiently to accommodate difficulties. For example, an employer may downgrade their responsibility, provide additional manual or clerical support, or incentivize goal achievement.

Conversely, the workplace can be an unforgiving environment in which vulnerabilities like reduced drive, initiative and spontaneity are exposed in public. Unsympathetic colleagues may resent someone not pulling their weight, and financial losses can follow. For these reasons, disorders of drive and motivation often underlie workplace difficulties or failure to make a successful return to employment, although they can easily be mistaken, especially during the course of litigation where there may be a disincentive to return to work. These difficulties can add to the emotional and financial burden of a family coping with the aftermath of brain injury.

DEVELOPMENTAL IMPLICATIONS

It is self-evident that if NBD's, of the kind elucidated above, occur during childhood, before maturational development is complete, then the process of development will be undermined and there is likely to be in insidious impact on the individual once middle teenage years are reached.

Neurons within the ventromedial prefrontal cortex (vmPFC) encode the emotional value of sensory stimuli in a way that is not only necessary for the normal generation of emotions, but how emotions develop and guide appropriate social behavior (133–136). Therefore, the developmental timing of TBI and the concurrent onset of deficits of emotional experience and expression including the lack of empathy described above (see section—"Failure of social cognition"), may also lead to more profound and serious psychosocial difficulties.

Impact on Social Judgement

Shamay-Tsoory et al. (137) and Shamay-Tsoory and Aharon-Peretz (138) proposed that the right vmPFC was necessary for the development of empathy which, in turn, is intrinsic to our understanding the emotions of others (social judgement). These studies noted that patients with lesions in the right vmPFC had a selective impairment that suggested a double dissociation between cognitive and affective theory of mind. Koenigs et al. (139) found that six patients with focal bilateral damage to the vmPFC exhibited an abnormally "utilitarian" pattern of judgements on moral dilemmas and reduced social emotions (such as compassion, shame and guilt) which are closely associated with the development of moral values (140, 141). An absence of emotional awareness has been associated with poorly regulated anger and low frustration tolerance without any loss of general intelligence, logical reasoning, or declarative knowledge of social and moral norms (142–144). Koenigs et al. (139) concluded that vmPFC damage diminishes the typical aversive affective response to harmful actions, reducing the impact of emotional control in the development of normal judgements to distinguish right from wrong. The affective functions of the vmPFC therefore seem necessary for normal moral judgement (145), bringing affect to bear on decision-making processes (146), reinforcing the key role of affect in the development of moral judgement (147).

Impact on Social Learning and Moral Development

Koenigs et al. (139) hypothesized that the vmPFC plays a critical role in the development of emotional learning and social or moral knowledge during childhood. Taber-Thomas et al. (148) also argue that the risk of moral impairment depends not just upon the location of brain injury but the stage of maturational development when the injury occurs. Many social skills emerge early in life (149), and represent important milestones in moral development (150, 151). The maturation of moral judgement, transitioning from selfish to social, has long been theorized as an essential marker of typical social and moral development (152, 153). Mosch et al. (154) and Trauner et al. (155) both found that damage acquired earlier in development leads to less severe cognitive outcomes but more severe impairments in social and moral reasoning (140, 148). Consequently, dysfunction of the vmPFC (on the neural side) and impaired empathy (on the psychological side) may play central roles in psychopathy, a neurodevelopmental disorder hallmarked by callous, manipulative, egocentric and impulsive antisocial behavior (156, 157).

Anderson et al. (140) reported on two cases of individuals with vmPFC injury acquired during early childhood who exhibited a lack of empathy and amoral behavior. The two patients were injured before 10 years of age and were 20 and 23 years old at time of follow up. Whilst their intellect, memory and language had developed normally, they exhibited impaired decision making and were unable to make realistic plans for the future. Their behavior was characterized by physical and verbal abuse, sexual irresponsibility, a lack of empathy for others and an egocentric perspective on the world. They failed to acquire social and moral knowledge and, as adults, exhibited moral reasoning appropriate for a 10 year old with no sense of guilt, remorse, or moral

responsibility. They exhibited—"*Behaviour akin to that of a psychopath*" (p. 1035), with asocial behavioral patterns more severe than those typically observed in patients with adult-onset vmPFC lesions.

The vmPFC may therefore be critical for the acquisition and maturation of moral faculties. It has been argued that a lack of moral development could be attributable to impaired aversive learning to self-serving moral transgressions based on complex social-emotional reinforcement contingencies [e.g., punishment for selfish behavior that is hurtful to others; (158–160)]; leading to an immature, abnormally egocentric moral sensibility. Damage that occurs later in life may not affect this early phase of moral development so severely, even though vmPFC damage acquired at any point in life is likely to impact upon the ability to integrate social-emotions (e.g., an aversion to harming others or to performing selfish actions) into reasoning about novel, complex moral situations (139, 148, 161, 162).

Failure of Moral Development and Risk of Offender Behavior

The evidence relating to abnormal moral development and sociopathic patterns of behavior after injury to the vmPFC in childhood may explain why such a high number of offenders in custody have a history of head/brain injury. Williams (163) reported prevalence rates for TBI in young incarcerated male offenders (average age 16 years) as high as 60%, while McMillan et al. (164) recently found that the prevalence of hospitalized head injury in prisoners (24.7 per cent; 1080/4,374) was significantly higher than a matched general population sample (18.2 per cent; 2394/13122). In a systematic review of youth offending, Hughes et al. (165) reported prevalence rates of brain injury amongst incarcerated youth of between 16.5 and 72.1 per cent. In addition, Pitman et al. (166) showed that almost half (47 per cent) of their sample of 613 adult male prisoners reported a history of TBI when screened on admission to prison. The majority (70 per cent) of offenders reported receiving their first injury prior to their first offense.

These studies reinforce the notion that TBI may be a risk factor for offending, based on an assumption that injury acquired during an early stage of development results in a subsequent failure of emotional awareness, leading to a lack of empathy and a failure of moral judgement, the consequences of which are diminished social cognition, poor social-interpersonal communication skills, poor control over the need for gratification, and an absence of guilt or responsibility about how their "needs" are gratified. Consistent with this, numerous studies have shown that adults who sustained TBI in childhood are significantly poorer at emotion perception than healthy controls, exhibit a greater frequency of externalizing behaviors, have poor pragmatic communication ability, experience greater behavioral problems (i.e., emotional lability, aggression, disinhibition), and get into more trouble with law enforcement (167).

CONCLUSION

To conclude, the way NBD presents clinically and socially across individuals can vary considerably because of the range of injury-related, personal and social factors, as well as the varying contributions made by cognitive, behavior and personality changes. Demographic factors, employment status, social and cultural factors, plus pre-injury psychiatric history and individual coping styles illustrate the complex interactions between factors that determine psychosocial outcome after brain injury, and how these need to be incorporated into a comprehensive programme of rehabilitation to support recovery. However, what is clear is that the presence of NBD after brain injury undermines social independence and can prevent survivors from achieving their full recovery potential. It has an adverse impact on a broad range of psychosocial functions and acts as a burden to both families and caregivers, potentially leading to increased social isolation, and, in more serious cases, gravitation to institutional placements for management purposes. In addition, as many social skills emerge early in life and represent important milestones in moral development, the age at which injury occurs should not be underestimated as an important consideration, as it can lead to further negative impacts, including an increased risk of offending. Therefore, more work on the often subtle but insidious nature of NBD during early maturational development is needed.

AUTHOR CONTRIBUTIONS

Each author was responsible for producing a first draft of a key section. CW social cognition. NA aggressive behavior. AW disorders of drive/motivation. RW developmental timing. CW and RW shared editorial responsibility throughout the drafting process. Final amendments were made by CW. All authors gave approval for submission, contributed significantly to the article, and are responsible for its contents.

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REVIEW
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Neurobehavioral Initiation and Motivation Problems After Acquired Brain Injury

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Motivation is a primary and permanent source of human behavior and adaptation. Motivational deficits, along with deficiencies in initiation, frequently occur in individuals with acquired brain injury (ABI). These neurobehavioral problems are associated with consequences at the participation level: patients are reluctant to engage in rehabilitation, and their subsequent social reintegration is often at risk. The same problems may also become a heavy burden for the families of individuals with ABI. In the present paper, we will critically review both the current definitions and the instruments used to measure motivational disorders following ABI. We will also describe the neural system underlying motivation and its impairments. What emerges is the need to develop specific rehabilitative treatments, still absent at the moment, with the ultimate aim of ensuring a better quality of life for both the patients and their proxies.

Keywords: initiation, motivation, apathy, adynamia, acquired brain injury

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INTRODUCTION

According to the World Health Organization (1), an acquired brain injury (ABI) is a brain lesion occurring after birth that cannot be related to a congenital or degenerative disease. Distressing physical and cognitive disabilities are well-known consequences of ABI. However, the ensuing changes in neurobehavioral functioning may even be more overwhelming for both the patients as well as their proxies (2).

Neurobehavioral disability (NBD) (3) is a term used to describe neuropsychological disabilities and behavioral disturbances in individuals with ABI (4). The concept was introduced to emphasize the idea that disorders of cognition, social behavior, emotional expression, and personality are connected in persons with ABI and may ultimately result in disrupted and provocative behavior. According to Wood (5), NBD may include executive and attentional impairments; lack of insight and awareness; social judgment problems; labile mood; inadequate impulse control; and several personality changes. These consequences of ABI undermine the capacity for independent social behavior and result in severe long-term social impairment, leading to poor psychosocial outcomes (6). Moreover, they affect not only the survivors of brain injury but also their whole families (2).

Within NBD and motivational deficits, lack of behavioral initiation is a consequence of ABI that proxies often report as the most difficult to deal with (7, 8). Initiation is a crucial aspect of motivation, as it represents the ability to start the execution of a task. But other features of motivation, like the paucity of goal directedness, may also be distressing and clinically significant. It is therefore important to define motivational disorders that afflict ABI survivors more clearly. This may contribute to the development of more adequate diagnostic tools as well as rehabilitation treatments that may lead to better living conditions for both the patients and those surrounding them.

MOTIVATIONAL DISORDERS IN ACQUIRED BRAIN INJURY SURVIVORS

Motivation contributes to adaptive functioning and is an important determinant of quality of life. It is the process that starts, regulates, and maintains goal-directed behaviors (9). Goal-directed behavior is composed of a set of associated processes (i.e., motivational, cognitive, emotional, and motor) allowing the achievement of a goal, by translating an internal state into action (10, 11). Such a goal might be immediate and physical, or long-term and abstract (11). As stated by Nevid (9): "Motives are the "whys" of behavior, the needs or wants that drive behavior and explain what we do."

Disorders of diminished motivation (DDM) are characterized by impairments in goal-directed behavior, thought, and emotion (12). These disorders occur frequently in individuals after an ABI: without apparent motivation, these individuals fail to stay on their medication, keep appointments, maintain interactions with their relatives and friends, or resume their jobs.

DDM can be clinically observed as a gross underproduction of speech, movement, and emotional response and include *akinetic mutism*, *abulia*, and *apathy* (13).

The most disabling condition within DDM is akinetic mutism. Akinetic mutism is characterized by an inability to voluntarily initiate motor or verbal responses, in the presence of preserved arousal and sensorimotor functions (14, 15). It is a severe clinical condition in which the person is totally deprived of motivation, devoid of primary needs, and characterized by a severe reduction of motricity, facial expressions, gestures, and verbal communication. However, these persons still retain some degree of alertness (16, 17).

Abulia, defined by Berrios and Gili (18) as a disorder of the will, is positioned in the middle of the spectrum of DDM. Although individuals with abulia show less severe symptoms than do persons with akinetic mutism, these symptoms are qualitatively identical: passivity, reduced spontaneous behavior and speech, lack of initiative, and psycho-motor slowing, combined with a reduced emotional responsiveness and spontaneity. According to Marin and Wilkosz (12), abulia results into akinetic mutism when it is exacerbated and into apathy when it is improved.

Apathy is a state of overt diminution in motivation, compared with an individual's previous state, although it is not related to cognitive, emotional, or motor deficits (19). It directly involves the person's goal-directed behavior, entailing a reduction of emotional engagement and a difficulty in initiating new actions (20). Marin and Wilkosz (12) purported that apathetic patients are able to start and pursue actions, report their intentions, and show emotional responses to major events. However, these behaviors are not as intense, less extensive, and shorter than in non-apathetic persons.

Levy and Dubois (21) have defined apathy as "the quantitative reduction of self-generated, voluntary and purposeful behaviors." They have identified three dysfunctional domains in apathetic individuals: the "affective-emotional" domain, in which an individual is incapable to establish a relation between emotional-affective expressions and ongoing or future behavior; the "cognitive" domain, which entails difficulties in devising a plan needed for ongoing or forthcoming behavior; and the "auto-activation" domain, which refers to the inability to activate and initiate thoughts and actions, combined with a relatively adequate skill to generate externally guided behavior. Deficits in auto-activation lead to a disruption in activation (also known as "psychic akinesia" or "athymhormia") and may be considered the most severe form of apathy (21).

Apathy is among the most common sequelae of ABI. There is no obvious relationship between the brain injury severity and the appearance of apathy. Moreover, apathy is generally unrelated to time since injury and has no significant association with either age at injury or educational level (22).

Prigatano (23) described the psychosocial problems associated with lack of motivation, also termed *amotivation* or *adynamia*, in patients with ABI. Amotivation and adynamia are related to the negative symptoms of apathetic behavior and anhedonia (24). Negative symptoms deal with behaviors, thoughts, or feelings normally present that are diminished or completely absent. It is also common that patients express a lack of motivation by reporting a decreased level of energy (anergia) or an abnormal physical or mental fatigue (24). As a result, these subjects may be seen as passive, apathetic, or depressed because they seem drained and uninterested in their environment. Anhedonia is defined as a consistent and marked reduction of interest or pleasure in previously rewarding activities (25).

Adynamia may result in considerable difficulties with new or more complex activities or behaviors, particularly those consisting of many steps, or entailing a sequence of steps to be achieved (26). So adynamia contributes to problems in many areas of life such as social functioning problems and difficulties in returning to work or study. It also negatively affects the learning of coping strategies and the application of skills trained during rehabilitation. Social isolation is commonly seen as a result of the patients' lack of motivation to interact with their environment (5). However, adynamia does not always means that persons feel unmotivated: although starting or completing a task is difficult, they often talk about their plans, goals, and planned activities. Individuals with adynamia often know what they want to do, but they lack the drive to actually start the activity (26). Some clinicians also use the term avolition for this symptom (24). The American Psychiatric Association (27) defined avolition as "a decrease in the motivation to initiate and perform self-directed purposeful activities." Hence, people with avolitional disorders encounter difficulties in initiating behaviors, although they can show these behaviors when verbally prompted to do so (24).

In this context, Laplane (28) introduced the concept of "loss of psychic self-activation" (LPSA) to describe a syndrome characterized by an almost complete lack of initiative, a strong reduction in spontaneous motor activity and speech, and an absence of self-initiated mental activity of any kind. A person with LPSA experiences a feeling of "mental emptiness," an indifference with regard to previous interests, and a flattened

affect (29). Strikingly, the absence of self-initiated activity may disappear in reaction to external stimulation (30). Thus, in some cases, verbal reminders and prompts are useful to stimulate individuals with ABI to start activities. However, additional cues are often necessary to stimulate patients to complete a task (26).

BRAIN REGIONS INVOLVED IN MOTIVATIONAL DISORDERS

Several empirical studies have revealed the involvement of subcortical–cortical circuits in the initiation of cognition and behavior. The generation of motivated behavior in healthy people involves a network of medial frontal and striatal regions (31).

In particular, the cortico-basal ganglia loop involving the ventral striatum (VS) plays a key role in the generation of motivational processes (32–35). The disruption of this loop produces akinetic mutism, abulia, or apathy (12). In this cortico-striatal-pallidal-thalamic circuit, the dorsal parts of the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC), the nucleus accumbens (NA), the ventral pallidum (VP), and the ventral tegmental area (VTA) are crucial areas in both the initiation and maintenance of adequate motivational levels [(24), see **Table 1** and **Figure 1**].

The involvement of some of these areas in motivated behavior has been confirmed by neuroimaging studies. These studies have shown that atrophy or functional disruption of the medial frontal cortex—in particular the dorsal ACC (dACC) and the OFC—are significantly related to apathy. Moreover, damage in subcortical areas such as the VS, the medial thalamus, and the VTA may also lead to apathy. Finally, disruption of the connections between all these regions contributes to apathy as well (24, 31). These brain–behavior relations have been established with several imaging techniques, including metabolic imaging methods. Gray matter (GM) atrophy findings and both structural and functional connectivity studies have confirmed these associations (31). The ACC and the VS seem to play an essential role in assessing and motivating choices that will lead to effort, and also in supporting the motivation required to sustain behavior until the attainment of a goal. Aversion to effort due to alterations in response within the ACC and VS may result in lack of motivation and therefore apathy (31).

The NA and the VP have more medial and lateral areas, which are connected to other different brain regions. Medial portions receive limbic input from the amygdala and the hippocampus, necessary to modify the current motivational state (32). The amygdala and hippocampus, as well as the prefrontal cortex (PFC), collect information from the current environment and the drive state of the organism, so as to modulate information in the circuit. In fact, neurons in these regions allow to record changes in the reward significance of the environment, and this could explain why damage to these brain structures presents as apathy (12). The involvement of the PFC in the occurrence of apathy after ABI has also been confirmed in group studies of patients with lesions in this area. In these studies, typical behavioral changes, such as impairments of goal-directed behavior and blunted affect, have been identified (36). In particular, the ventromedial PFC (vmPFC), including the OFC, has been mainly associated with valuation, reward learning, emotional regulation, and decision making, whereas the lateral PFC has a key role in executive control or the ability to synchronize thoughts and actions with internal goals, a process leading to effort (11). Paradiso et al. (37) even found that individuals with lateral prefrontal damage showed more symptoms of apathy than those with medial frontal damage, suggesting that damage to this area may also severely disrupt motivation. However, the ability to feel and report negative emotions was intact in these patients. Apathy in the traumatic brain injury (TBI) population may also be due to the dysfunction of another cortical area, the insula (11). The anterior insula, through its connections with the amygdala,

TABLE 1 | Cortical and subcortical regions and their putative contribution to motivational processes.

Cortical	Subcortical	Process
	- Amygdala (Am) - Hippocampus (Hc)	- Collect internal and external information (motivational input)
- dorsal Anterior Cingulate Cortex(dACC)	- Ventral Striatum (VS)	- Assess and motivate choices leading to effort
- Orbitofrontal Cortex (OFC)		- Update the value of choices
- lateral Prefrontal Cortex (lPFC)		
	- Nucleus Accumbens (NA)	- VTA + medial NA-VP: receive limbic input from Am and Hi
	- Ventral Pallidum (VP)	
	- Ventral Tegmental Area (VTA)	- VTA + ventral NA-VP: transmit to motor output systems (motor cortex, basal ganglia,…)

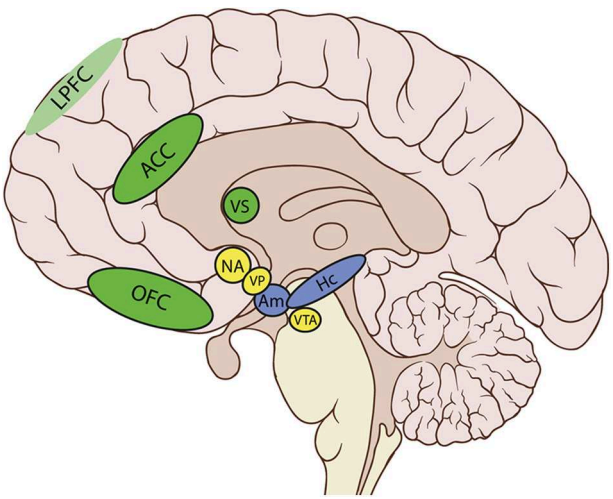

FIGURE 1 | Anatomical areas involved in motivation.

hippocampus, ACC, and OFC, computes higher-order meta-representations of the primary interoceptive activity. This activity is related to the feeling of pain and its emotional awareness (38). Therefore, damage to insular areas may result in decreased motivation, due to an absence of awareness of emotional and motivational feelings (11).

Through the motor cortex, the reticulospinal tract, the pedunculopontine nucleus, and the basal ganglia (BG), the lateral portions of NA and VP, are connected to output circuits. The BG are involved in many aspects of goal-directed behavior, including the control of movement, and also in mechanisms that drive actions, such as cognition, emotions, and motivation (39). BG are probably a crucial network underlying motivational processes, whereby expected rewards trigger the occurrence of behavior without requiring the persons' awareness (11).

The involvement of the above-described circuit in the occurrence of apathy after ABI has also been confirmed by a study in which event-related potentials (ERPs) were used to investigate the neuronal mechanisms underlying apathy (40). As expected, the authors found changes in the amplitude of the novelty P3 wave, correlated with apathy severity and occasioned by disturbances in the fronto-subcortical circuit.

Levy and Dubois (21) identified several clinical phenotypes of apathy and speculated that different parts of the segregated PFC–BG circuitry may represent the substrate of these phenotypes. The authors link "emotional affective apathy" with damage to the orbitomedial PFC and the VS. Moreover, they associate "cognitive apathy" with a defective functioning of the lateral PFC areas and the dorsal caudate nuclei. Finally, they hypothesize that a deficit of "auto-activation" may be associated with bilateral lesions of the internal parts of the globus pallidus, bilateral paramedian thalamic lesions, or damage to the dorsomedial PFC.

LPSA has more often been explained by a disruption of the frontal–subcortical circuit that underlies motivation (21, 41), including bilateral lesions of the BG, mainly affecting the caudate, pallidus, and putamen (42, 43).

On a more severe level, abulia may result from the disruption of the neural network involved in task initiation, which incorporates the ACC, bilateral anterior insulae, and the bilateral anterior thalami (14, 44). Akinetic mutism has been found to be associated with lesions to of the AC, either unilaterally or bilaterally (45).

ROLE OF DOPAMINE AND NOREPINEPHRINE IN MOTIVATIONAL DISORDERS

The pathogenesis of behavioral motivation problems after ABI may also be explained by a neurochemical disruption of the motivational circuitry. Dopamine (DA) seems to be the major neurotransmitter linked to motivation (24). Disorders of the mesolimbic DA system may reduce the capacity of stimuli to activate motivated behavior on hedonic bases, to poor activation and defective directional aspects of motivation for the initiation and constancy of behavior, and to an erroneous learning and evaluation of the costs and benefits of actions (46). DA activity, especially in the striatum, plays a central role in "reward, novelty seeking and response to unexpected events" (12). A reduced synthesis of DA attenuates sensitivity to rewards during decision making (24), whereas increasing levels of DA stimulate incentivization by rewards, and also the readiness to go beyond effort costs (31). Therefore, dysfunction of the mesolimbic and neostriatal DA projection systems may provoke impairments in reward-based decision processes. These processes regulate the motivational load that sustains frontal cognitive processes involved in determining goal-directed behavior (47). All these studies emphasize that motivation strongly relies on dopaminergic activity, which often appears to be affected in ABI (12).

Clinically, DA-based medication has been used in the treatment of a wide range of motivational disorder in patients with TBI (48–50). Anecdotal reports seem to show the benefits of these drugs, but according to Worthington and Wood (22), better-quality trials are needed to support these effects.

Beside DA, norepinephrine may also play a crucial role in the generation of adequate levels of motivation. The so-called noradrenergic system is an important regulator of arousal, and adequate levels of motivation are dependent on appropriate levels of arousal (51). Norepinephrine is mainly released by the locus coeruleus in the brainstem and projects throughout the brain. It affects brain functioning in several ways, by enhancing the processing of sensory stimuli, elevating attentional levels, intensifying the formation of memories, and reinforcing the tendency of the brain to respond to external and internal stimulation. These processes act as prerequisites for the adequate regulation of motivational levels and the initiation of behavior.

Another neurotransmitter linked to motivation is serotonin (24). Depletion of this neurotransmitter changes the attitude of people toward rewards and punishments, whereas administration of a serotonin reuptake inhibitor can influence decision making.

ASSESSMENT OF DISORDERS OF DIMINISHED MOTIVATION

As suggested by Spiegel et al. (13), the assessment of patients with diminished motivation should be structured, consider input from both patient and caregiver, and also include the physician's opinion. It should include a complete and systematic neuropsychiatric evaluation, including a picture of the patient's social and physical environment. It is important to investigate the psychosocial history to determine the patient's premorbid levels of motivation and coping skills and to take into account external factors like personal experience or education (12). It is also useful to obtain reports from multiple informants, including both the patient and significant others (11), as some studies have shown that apathetic patients report more severe apathy than do their relatives (52, 53).

To quantify the loss of motivation, several rating instruments have been developed. In a review, Clarke et al. (54) discussed 15 apathy scales or subscales and recommended the "Apathy

Evaluation Scale" (AES) and the "Neuropsychiatric Inventory" (NPI) as the most psychometrically robust.

The AES (55) is probably the most widely used assessment instrument. It consists of 18 items and can fill in as a self-rating scale, as caregiver paper-and-pencil test, and a semistructured inventory completed by the clinician (12). The NPI is also extensively used as a valid and reliable instrument. It consists of an interview, administered to the patient's caregiver, and is intended to identify the existence and the severity of 10 non-cognitive symptoms, including apathy (12, 13, 56).

More recently, Ang et al. (57) have introduced the Apathy-Motivation Index (AMI), a reliable short self-report scale designed for assessing motivation and measuring individual levels of apathy. The AMI is a useful instrument to survey different processes underlying deficiencies of motivation in otherwise healthy people. This scale uncovers associations between apathy and comorbid problems in different emotional, social, and behavioral domains.

Alterations in motivation can also be assessed by examining a patient's reactivity to internal or external stimulation (58). The need to design more objective tools to evaluate apathy has led Muller et al. (52) to log everyday motor activity in patients with acquired brain damage. The extent of apathy is assessed by measuring the rate of self-initiated behavior. This type of instrument allows to relate the signs of apathy to the performance in other behavioral and cognitive tasks. Examples of behavioral tasks include gambling or reversal tasks investigating the ability to adapt behavior in function of expected rewards. The Wisconsin Card Sorting Test, the Tower of London test, or fluency tests are examples of useful instruments to establish a relation between apathy and cognitive inertia (59).

REHABILITATIVE INTERVENTIONS

Given the frequency of severe motivational symptoms in patients with ABI and the problems they bring about in terms of loss of social participation, economic and occupational cost, and especially caregivers' well-being, it seems extremely important to develop adequate rehabilitation interventions to alleviate these personal and social costs and to ensure a better quality of life for both the patients and their proxies.

Unfortunately, specific treatments for initiation and motivation problems after ABI are rare and often not evaluated in well-designed studies. In most of the cases, psychological treatments are not specifically designed for initiation or motivation problems, and they generally incorporate a variety of specific cognitive rehabilitative techniques, or behavioral modification methods, or both (12, 60, 61). Cognitive rehabilitation therapies utilize techniques found in problem-solving therapy, based on strategies to improve goal-directed behavior by teaching better planning, execution, and monitoring of activities (61). Other cognitive interventions use external compensation strategies like checklists and paging systems to stimulate initiation toward goal-directed activities (62).

Examples of behavioral therapies are activity therapy (63), multi-sensory stimulation (64), and music therapy (65). These therapies have been shown to diminish apathy to some extent in neurological populations with progressive disorders, in particular Alzheimer's dementia. However, a majority of these studies lack rigorous designs for unbiased evaluation of treatment effects. Therefore, the obtained results may actually be due to factors such as spontaneous recovery of apathy, rater expectations of gains, or non-specific effects, given the frequent lack of a control group. Another widely used behavioral technique is goal-setting therapy (61), which consists in using goals to provide targets for patients to work toward (66). Goal-setting therapy is based on the idea that explicit goals trigger action (67) and that conscious human behavior is directed and driven by individual goals. The technique allows targeting of individual goals and effects to be readily measured (68). To this date, only one study (69) used goal setting in a neurological population. In a sample of 100 patients, 78% of the long-term goals set by the participants were achieved, indicating that goal-directed activity was successfully accomplished. On the other hand, in a study with brain injury subjects comparing cognitive behavioral therapy (CBT) and a peer support group (70), no significant improvements in functioning were found for either group on the subscales "executive dysfunction" and "apathy" of the Frontal Systems Behavior Scale. It is clear that further studies, specifically investigating the effectiveness of apathy treatment in individuals with ABI (of non-progressive nature), are needed.

In apathy, communicative and cognitive skills are often preserved, and therefore, psychological and social interventions are the treatments of choice. On the other hand, the treatment of more severe disorders like akinetic mutism and abulia is mainly pharmacological (12). Pharmacological interventions are often based on the prescription of DA agonists (71). Several studies suggest that the use of acetylcholinesterase inhibitors and psychostimulants may also be effective in the pharmacological improvement of apathy (61, 72).

Although specific treatments are scarce, some general recommendations concerning rehabilitation of apathy have been made. First of all, it is indispensable to optimize the patient's general medical condition, which contributes to positive effects on motivation (12). The improvement of general physical condition can enhance functional skills, energy, and drive, thus increasing the patient's expectation that taking initiatives and sustaining efforts may lead to the attainment of behavioral goals.

The treatment of neurobehavioral motivation problems after ABI should be based on thorough assessment, followed by an estimation of a patient's losses and residual capacities (73). This allows the design of "psycho-prostheses" that enable patients to compensate for their deficits and help them to make the best possible use of their residual capacities (12).

Target behaviors and baseline frequencies should be identified prior to treatment (73), and therapeutic goals should be established in collaboration with the patient, to reinforce engagement and intensify the patient's feeling of control and belief in success (12). It is important to make use of personalized treatments (24) —pharmacological or psychological—and to also pay attention to the physical and psychological determinants of apathy (73).

Other important variables contributing to effective treatment are the modification of the patient's environment and the participation of family members and professional therapists in the treatment of DDM (12). The objective of environmental interventions is to strengthen the rewarding potential of the environment, by introducing new of familiar sources of interest, pleasure, stimulation, and also socialization. Finally, psycho-education, professional counseling, and psychotherapy interventions should not be overlooked, as they may help in dealing with injury-related losses, interpersonal problems, or family stressors related to individual determinants of initiation and motivation problems (12).

However, methodologically more rigorous studies have to be designed and performed in order to investigate the effectiveness of different treatment techniques aimed at improving initiation and motivation problems after ABI. In particular, more randomized controlled trials comparing the different ways of addressing apathy are required. These trials should be conducted with larger sample sizes than those of the studies already carried out. Furthermore, the use of more sophisticated research designs and appropriate statistical analyses are needed to examine both the effects of therapies and the differences between groups of patients with distinct types of brain injuries. In order to compare treatments and their implementability, a more standardized terminology and better operationalized definitions of motivation and initiation disorders are also required.

CONCLUSIONS

Motivation is a ubiquitous and crucial determinant of behavior and adjustment. Deficits in self-initiated, goal-directed motivated behavior are common after ABI, representing one of the most draining legacies of the injury for the patient and for his/her proxies. These deficits seem to be related to malfunctioning of DA activity and to dysfunction of a network of medial frontal and striatal regions. Current knowledge of the normal function of these brain areas in motivated behavior allows straightforward and hypothesis testing approach to DDM, with predictions that can be verified.

Although some promising tools for assessing apathy are currently available, in the field of treatment, an unsatisfactory and worrying situation emerges. For the time being, there are only generic recommendations but no evidence-based specific interventions that support a targeted treatment of initiation and motivation problems for patients with ABI.

The goal of future research should be to better define and operationalize the constructs of motivation and initiation disorders. These may contribute to design increasingly valid assessment tools, with the ultimate aim to develop effective and personalized treatments for patients suffering from these disabling symptoms. By improving treatments, it will be possible to offer persons with ABI a way to improve their functional capacities and thus to ensure a better quality of life for both the patients and their proxies.

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GLOSSARY

- Abulia: a less severe type of apathy than akinetik mutism, characterized by lack of initiative, passivity and a reduction of verbal and motor responses.
- Adynamia: a decrease of vital power that leads to a lack of behaviour, thought and feeling normally present.
- Akinetic mutism: the most severe form of apathy, in which a person does not show motor or verbal responses anymore, despite a relatively preserved alertness.
- Avolition: a lack of motivation necessary to start and accomplish purposeful tasks.
- Apathy: a reduction of self-generated, purposeful behavior.
- Anhedonia: a marked decline of pleasure in activities that were previously rewarding.
- Loss of Psychic Self-Activation (LPSA): a striking loss of self-initiated behaviours coupled with a feeling of mental emptiness, but with normal reactivity to external stimulation.
- Motivation: the needs and wants that fuel behaviour and explain why a person behaves in a certain way.
- Neurobehavioural Disabilities (NBD): a mixture of disorders of cognition, social behaviour, emotional expression and personality that may result in disrupted and provocative behaviour after Acquired Brain Injury.

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The Spectrum of Long-Term Behavioral Disturbances and Provided Care After Traumatic Brain Injury

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Timmer ML, Jacobs B, Schonherr MC, Spikman JM and van der Naalt J (2020) The Spectrum of Long-Term Behavioral Disturbances and Provided Care After Traumatic Brain Injury. Front. Neurol. 11:246. doi: 10.3389/fneur.2020.00246

Introduction: Behavioral disturbances are found in 50–60% of traumatic brain injury (TBI) survivors with an enormous impact on daily functioning and level of recovery. However, whether typical profiles can be distinguished and how these relate to provided care is unclear. The purpose of this study is to specify the characteristics of behavioral disturbances in patients with various severity of TBI and the impact on functional outcome. Furthermore, the pathways of care after hospital discharge for patients and their care givers are analyzed.

Methods: We performed a retrospective cohort study comprising 226 patients with mild TBI (mTBI; $n = 107$) and moderate-to-severe TBI (mod/sevTBI; $n = 119$) treated at the outpatient clinic and/or rehabilitation center of our university hospital between 2010 and 2015. Inclusion criteria were: behavioral disturbances as determined with the Differential Outcome Scale and age $\geq$16 years. Functional outcome was determined by the Glasgow Outcome Scale Extended and return to work (RTW) at six months to one year post-injury. Behavioral impairments and pathway of care were derived from medical files and scored according to predefined criteria.

Results: Overall 24% of patients showed serious behavioral disturbances; three times higher in mod/sevTBI (35%) compared to mTBI (13%). mTBI patients mostly showed irritation (82%) and anger (49%), while mod/sevTBI patients mostly showed irritation (65%) and disinhibition (55%). Most (92%) patients returned home, half of the patients did not RTW. Deficits in judgment and decision-making increased risk of no RTW 10-fold. One in ten patients was (temporarily) admitted to a nursing home or psychiatric institution. 13% Of caregivers received support for dealing with impairments of patients and 13% of the mTBI and 17% of the mod/sevTBI patients experienced relational problems.

Conclusions: The spectrum of behavioral disturbances differs between TBI severity categories and serious behavioral disturbances are present in a quarter of patients. Only half of the patients resumed work regardless of severity of injury suggesting that

particularly the presence and not the severity of long-term behavioral disturbances interferes with RTW. Most patients returned home despite these behavioral disturbances. These findings underline the importance of early identification and appropriate treatment of behavioral disturbances in TBI patients.

Keywords: behavioral disturbances, traumatic brain injury, outcome, return to work, discharge destinations, caregivers

INTRODUCTION

Traumatic brain injury (TBI) is a public health problem worldwide and an important cause of neurological and psychosocial dysfunction (1, 2). The estimated incidence of TBI in Europe is 235/100.000 cases per year (3). The severity of TBI is generally determined by using the Glasgow Coma Scale (GCS) and is characterized as mild, moderate or severe TBI. A large number of TBI survivors, especially those with moderate to severe TBI (mod/sevTBI), has permanent impairments regarding the physical, cognitive and behavioral domains and social functioning (4–6). Behavioral disturbances interfere with daily life and social interaction and vary from apathy, disinhibition, and agitation, to aggression and violent behavior, that frequently exist simultaneously (7, 8). These behavioral disturbances are in general difficult to manage due to impaired self-awareness and may still be present several years after trauma (9–11). In severe TBI behavioral disturbances have been found in 50–60% of survivors with an enormous impact on participation, in particular vocational and family functioning (12–16) but limited information is available on the presence and effect of behavioral disturbances in mTBI patients. It is known that frontal CT-abnormalities are associated with long-term neurobehavioral changes in mod/sevTBI (17) and that lesions in the prefrontal and temporal cortex are associated with aggression, violence, and apathy (18, 19). In mild TBI (mTBI) however, not the location of the lesion but duration of post traumatic amnesia is the most consistent predictor for behavioral impairments post-trauma (20).

After discharge from the hospital, different pathways of care emerge for patients with TBI, but it is unclear how healthcare is provided specifically for TBI patients with behavioral disturbances. The usual rehabilitation pathway for TBI patients is not suitable for some patients due to serious behavioral disturbances and impaired self-awareness and they are therefore either discharged prematurely to their homes or admitted to a nursing home or psychiatric institution (21). It has been shown that several years post-trauma 10% of TBI patients still visit a psychiatrist (22). Behavioral disturbances in TBI patients also affect the lives of their caregivers and significant others (23, 24). In a previous study half of these caregivers reported elevated distress with the severity of injury associated with family burden (15). Therefore, when evaluating long term behavioral disturbances the effect on caregivers has to be taken into account simultaneously (13).

The purpose of the current study is to identify common characteristics of behavioral disturbances in patients with TBI of various severities and to determine the association with long term outcome and return to work. A second aim is to investigate the pathways of care provided for TBI patients with behavioral disturbances, in order to evaluate which care is provided and whether this relates to outcome. Furthermore, we want to identify the impact of behavioral disturbances on their caregivers and significant others, while this is an important aspect of outcome that is not assessed with the frequently used questionnaires determining functional outcome, like the Glasgow Outcome Scale.

METHODS

Participants

All adult TBI patients (aged $\geq$16 years) with post-traumatic behavioral disturbances who were treated between 2010 and 2015 at the University Medical Center Groningen (UMCG) or the UMCG Center for Rehabilitation Beatrixoord, were included if the injury had occurred in 2005 or later. Patients with disturbances based on their score on the behavorial domain of the Differential Outcome Scale (DOS) (explained below), as registered in the prospective Neurotrauma Database of our department, were included. The following demographic and clinical variables were used for analysis: age and gender, medical history with psychological or psychiatric disorder(s), substance abuse and previous TBI, severity of TBI (duration of loss of consciousness (LOC)/posttraumatic amnesia (PTA), initial Glasgow Coma Scale (GCS) score, admission to ICU, total duration of admission to the hospital).

Based on the GCS score (25), two TBI severity groups were defined: 1. Mild TBI (GCS 13-15; mTBI) and 2. Combination of moderate (GCS 9-12; modTBI) to severe (GCS $\leq$ 8; sevTBI) TBI. Structural traumatic brain damage was evaluated by CT and/or MRI scanning performed directly after trauma or during follow-up. The location of lesions was scored as frontal, temporal, fronto-temporal, and parieto-occipital. Information on caregiver burden and/or support and relationship problems was derived from the medical charts. This study was performed in compliance with the ethical regulations of our institute.

Measures

Time of assessment varied depending on severity of injury: for mTBI this was in general after six months and in mod/sevTBI this was in general one year post-injury. In general for mild TBI

the outcome endpoint is reached at six months post-injury and for mod/sevTBI this is at one year after trauma. (26, 27).

Severity of Behavioral Disturbances

Differential Outcome Scale (DOS) (28): The DOS scale categorizes outcome in four domains: neurophysical, cognitive, behavioral, and social. The DOS behavioral subscale (DOS-BS) has five categories, ranging from 5 = complete recovery or minor changes, 4 = mild changes, noted by experts or by those who knew the patient before the injury, 3 = obvious changes, noted by laymen who did not know the patient before the injury, 2 = severe personality changes and 1 = persistent vegetative state. Patients with a DOS-BS score between 2-4 were included in the study. DOS scores were obtained at the out-patient clinic of the Neurology Department of our hospital during follow-up within one year after injury. For logistic regression analysis, a dichotomy was used: mild behavioral disturbances (DOS-BS = 4) and serious behavioral disturbances (DOS-BS = 2–3).

Characteristics of Behavioral Disturbances

To identify behavioral disturbances data from the medical files were used, including neuropsychological examinations, reports of out-patient visits and admission reports of rehabilitation physicians and neurologists. Behavioral disturbances were scored on the following characteristics of behavior: inhibition, wandering behavior, different aspects of anger (with increasing severity order: irritation/agitation, anger, verbal aggression and (physical) violent behavior), apathy and/or less responsive affectionate behavior. Furthermore, the presence of impaired self-awareness, deficits in judgment and decision making and planning, and regulation disorders were noted. The different characteristics of behavioral disturbances were scored as present when they were as such described in the medical file notes from out-patient visits and/or reports of neuropsychological examinations, which could have been recorded at any time during the whole period of follow-up till the final outcome measurement.

Functional Outcome

Glasgow Outcome Scale Extended (GOSE) (29): The GOSE is an eight point scale to determine the overall functional outcome with 8 = upper good recovery, 7 = lower good recovery, 6 = upper moderate disability, 5 = lower moderate disability, 4 = upper severe disability, 3 = lower severe disability, 2 = vegetative state and 1 = death. For statistical reasons we dichotomized functional outcome in favorable versus unfavorable outcome. To compare mTBI and mod/sevTBI properly, we chose one cut-off point: favorable outcome was defined as GOSE 5-8 and unfavorable as GOSE 1-4 (30). Normally, in mTBI a favorable outcome is defined as GOSE 7-8.

Return to Work

Return to work (RTW) (31) was classified into seven categories: 0 = previous job or study resumed, 1 = previous job or work resumed, but with lower requirements or part-time, 2 = simplified job or study at significant lower level, 3 = not working – no study/declared unfit, 4 = not working, nursing home/mental institution, 5 = not to judge, rehabilitation program and 6 = retired. Work resumption was defined by RTW 0-1 and incomplete work resumption was defined by RTW 2-5. Pre-injury retired or incapacitated patients were not included in the RTW-analysis.

Evaluation of Pathways of Care and Out-Patient Follow-Up

Information on the care provided for patients was derived from medical files as well. The "primary hospital" was defined as the hospital to which the TBI patients were admitted directly after injury at the emergency department. Discharge destinations from the primary hospital or so called next level(s) of care were scored into five categories: home, regional general hospital—called "secondary hospital" in **Figure 1**, rehabilitation center, nursing home and psychiatric institution. The final professional care provider was defined by the last physician or therapist, next to the general practitioner, that treated the patient with persistent complaints in the chronic phase: psychiatrist, (neuro)psychologist, social worker, specialized nurse, neurologist, rehabilitation specialist or other care providers. The effect of behavioral disturbances on caregivers was measured in two ways: we registered the professional care provided for the experienced burden by care givers and whether relations of patients with their significant others had changed. As caregivers were regarded those persons that were directly responsible for the care of patients i.e., spouses, parents or children.

Statistical Analysis

For statistical analyses Statistical Package for the Social Sciences (SPSS) version 23.0 was used. Pearson's Chi-square and Fisher's exact tests were performed for frequency analysis and unpaired t-tests were performed for differences between continuous variables (p-value < 0.05). Correlations between different outcome variables were calculated by Pearson correlation coefficients. Univariate binary logistic regression analysis was used to identify demographic, clinical (including behavioral characteristics) and radiological variables (mentioned above) associated with outcome parameters defined by dichotomized GOSE, DOS-BS and RTW scores. Significant variables (p-value < 0.05) from the univariate analysis were analyzed in multivariate logistic regression analysis with forward likelihood ratio selection, for GOSE, DOS-BS and RTW respectively. These analyses were performed for each of the severity subgroups (mTBI vs. mod/sevTBI) separately.

RESULTS

In total 226 patients with behavioral disorders after TBI were included in this study: 107 patients with mild TBI and 119 patients with moderate ($n = 45$) to severe ($n = 74$) TBI. Patient characteristics are presented in **Table 1**.

Overall 24% of patients showed serious behavioral disturbances (DOS-BS 2-3) and 76% showed mild behavioral disturbances (DOS-BS 4), with serious behavioral disturbances almost three times more present in severe TBI (35%) compared to mTBI patients (13%) (**Table 2**). Irritation and agitation were

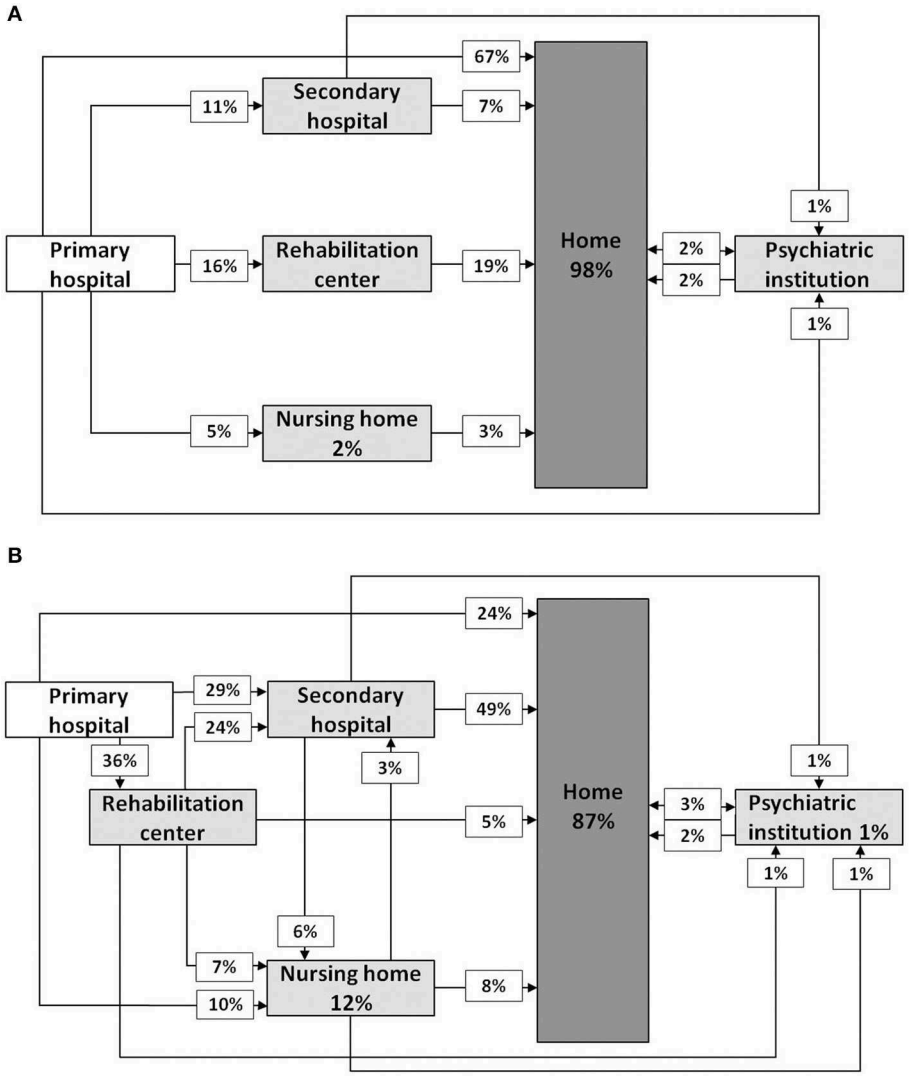

FIGURE 1 | Schedule representing pathways of care after mild TBI **(A)** and moderate to severe TBI **(B)** in case of behavioral disturbances. Percentages are rounded to whole numbers.

the most prevalent behavioral disturbances in mTBI (82%) and half of the patients additionally showed anger (**Table 3**). Most patients with mod/sevTBI were also irritated or agitated (65%), and more than half of the patients showed disinhibited behavior (55%). We found no significant gender differences in the presence of the different behavorial disturbances, only the difference in anger was significant occurring in 34% (21/61) of females and in 49% (79/160) males (Chi-square 3.984, $p = 0.046$).

Overall (Functional) Outcome

Favorable outcome (GOSE 5-8) was present in 96% of mTBI and in 24% of mod/sevTBI patients. Only about a half of all patients in both groups was able to return to previous work or study completely or part-time, with no significant difference between severity groups. No significant differences were present for GOSE scores and RTW between males and females (favorable outcome in 25 and 17%, Chi-square 1.478, $p = 0.289$) and RTW in 62 and 57% respectively (Chi-square 0.301, $p = 0.625$).

Associations With Outcome Variables

Significant correlations were present between presence of behavioral disturbances (DOS-BS) the overall GOSE outcome score ($r = 0.22$; $p < 0.01$) and RTW ($r = 0.41$; $p < 0.01$) in mTBI. Even stronger correlations were found in mod/sevTBI between the DOS-BS and the GOSE outcome score ($r = 0.52$; $p < 0.01$) and RTW ($r = 0.55$; $p < 0.01$).

Univariate regression analyses did not show associations between the localization of brain lesions and GOSE, RTW, or DOS-BS. Variables that were significantly associated with the outcome variables (DOS-BS, GOSE, RTW) after univariate analysis (data not shown) were included in a multivariate logistic regression analysis. The individual behavioral characteristics

TABLE 1 | Patient characteristics.

Patients characteristics	mTBI $n = 107$	mod/sevTBI $n = 119$	*p*-value
Male/female ratio	71/29	72/28	0.836
Mean age at injury (SD)	45 (17)	43 (18)	0.346
Range	17-88	16-81	
Pre-injury mental problems (%)	7.5	8.4	0.797
Mechanism of injury (%)			0.121
Traffic accident	34	48	
Fall	52	45	
Violence	4.0	2.0	
Other	10	5.0	
Hospital admission (in days)			0.000
Mean (SD)	10 (12)	31 (21)	
Range	0-51	1-147	
IC admission (in days)			0.000
Mean (SD)	2.1 (5.8)	12 (11)	
Range	0-33	0-46	
CT and/or MRI lesions (%)			
None	43	20	0.000
Frontal	44	61	0.018
Temporal	27	50	0.001
Fronto-temporal	4.7	6.7	0.532
Parietal-occipital	13	14	0.839
Missing	2.8	0.8	

mTBI, mild traumatic brain injury; mod/sevTBI, moderate to severe traumatic brain injury; SD, standard deviation; IC, intensive care; CT, computed tomography; MRI, magnetic resonance imaging.

TABLE 2 | Outcome scores.

	mTBI		mod/sevTBI		p-value
	%	*n*	%	*n*	
Outcome GOSE					0.000
Favorable (5-8)	96	103	76	91	
Unfavorable (1-4)	4.0	4	24	28	
DOS behavior					0.001
Mild (4)	87	93	65	78	
Serious (2-3)	13	14	35	41	
Return to work					0.055
Yes (0–1)	53	57	51	61	
Low level/ not (2-5)	32	34	36	43	
Retired	12	13	11	13	
Missing	2.8	3	1.7	2	

mTBI, mild traumatic brain injury; mod/sevTBI, moderate to severe traumatic brain injury; GOSE, Glasgow Outcome Scale Extended; DOS, Differentiated Outcome Scale.

were not analyzed with DOS-BS as dependent variable, because of obvious overlap. In mTBI multivariate analysis showed associations between DOS-BS as dependent variable and pre-injury mental health problems and substance abuse (**Table 4**).

TABLE 3 | Characteristics of behavioral disturbances.

Behavioral disturbances*	mTBI (%)	mod/sevTBI (%)	*p*-value
Disinhibition	33	55	0.001
Wandering behavior	3.7	7.6	0.218
Different aspects of anger*	82	65	0.003
Irritation/agitation	82	65	0.003
Anger	49	40	0.224
Verbal aggression	11	10	0.796
Physically violent	1.9	0.8	0.504
Apathy	26	35	0.164
Less responsive affectionate behavior	3.7	3.4	0.878
Impaired self-awareness	11	30	0.000
Deficits in judgment and decision making	12	22	0.038
Planning and regulation disorder	36	41	0.256
Loss of decorum	5.6%	17%	0.002

**Not mutually exclusive.*
mTBI, mild traumatic brain injury; mod/sevTBI, moderate to severe traumatic brain injury.

TABLE 4 | Multivariate logistic regression analysis.

	Dependent variable	Independent variable	OR	95% C.I.	p-value
mTBI	DOS-BS	Substance abuse in history	11.8	1.61;85.7	0.015
		Psychological/ psychiatric history	7.06	1.09;45.7	0.040
	GOSE	Age (years)	1.26	1.04;1.51	0.016
	RTW	Deficits in judgment and decision making	10.1	2.03;50.4	0.005
mod/ sevTBI	DOS-BS	Duration hospital admission (days)	1.03	1.00;1.05	0.010
	GOSE	Duration hospital admission (days)	1.10	1.02;1.18	0.010
	RTW	PTA duration (in days)	1.08	1.03;1.14	0.001
		Deficits in judgment and decision making	12.3	1.00;153	0.050

mTBI, mild traumatic brain injury; mod/sevTBI, moderate to severe traumatic brain injury; DOS-BS, Differentiated Outcome Scale – Behavioral Subscale; GOSE, Glasgow Outcome Scale Extended; OR, odds ratio; C.I., confidence interval.

GOSE as dependent variable was significantly associated with age. RTW was significantly associated with the behavioral characteristic of deficits in judgment and decision-making.

In mod/sevTBI DOS-BS and GOSE were significantly associated with the total duration of hospital admission. RTW was associated with PTA duration and comparable to mTBI with deficits in judgment and decision making.

Pathways of Care and Final Care Providers

Figure 1 shows the pathways of care for patients with mTBI and for mod/sevTBI separately. Three patients were not included due to missing data. In total 117 patients were given rehabilitation therapy either during admission at a rehabilitation center or at the out-patient clinic. Patients following a rehabilitation program

TABLE 5 | Care providers for patients in the acute and chronic phase post-injury.

	Acute phase		Chronic phase	
	%	*n*	%	*n*
Rehabilitation physician	52	117	65	147
Neurologist	66	148	62	139
Psychiatrist	7	16	11	25
Psychologist	26	59	52	117
Social worker	7	16	11	25
Specialized Nurse	17	38	9	20

The acute phase is defined as the period between 6 weeks and 6 months after injury. The chronic phase is defined as the period 6–12 months post-injury.

showed in 54% a favorable outcome compared to 47% in patients without active rehabilitation, with 60% RTW versus 61% RTW respectively.

In mTBI four patients (4%) and in mod/sevTBI six patients (5%) were eventually admitted to a psychiatric institution, from which one patient stayed permanently in a psychiatric institution and two patients suffered from a severe depression. Both for mTBI and mod/sevTBI the psychologist or psychiatrist was in one in four patients the final care provider. In the chronic phase half of the patients was treated by a psychologist and more than 10% by a psychiatrist (**Table 5**). No differences regarding care providers were found for patients with mild versus serious behavioral disturbances. Eventually, 92% of the patients returned home, despite serious behavioral disturbances in a substantial proportion of the patients. Patients who stayed permanently in a nursing home all had serious behavioral disturbances.

Care Givers

In mTBI almost 13% of the patients developed relational problems, and in half of these cases the relations with their significant others were ended. In mod/sevTBI the percentage of disrupted relations was 17%, from which one third was ended. A small but significant correlation was present between the presence of behavioral disturbances and occurrence of relational problems (rho=0.23 $p < 0.01$).

In both mTBI and mod/sevTBI 13% of the caregivers received support for dealing with the impairments of the patients. This support was highly variable from a psychologist to a social worker, psycho-education group, peer support and/or family counseling. Caregivers of mod/sevTBI patients mostly received support from a psychologist (3%) or a social worker (2%) and those in the mTBI group mostly from a social worker (3%), psychologist (2%) or peer group (1%).

DISCUSSION

The first aim of the current study was to investigate the specific characteristics of TBI patients with behavioral disturbances and their relation to outcome. In 24% of these patients the behavioral disturbances were serious and in moderate to severe TBI serious behavioral disturbances occurred three times more than in mild TBI. A different spectrum of behavioral disturbances was found in mTBI compared to mod/sevTBI. These disturbances had a large impact on functional outcome and social life: regardless of severity of injury, half of all patients could not resume their work. Furthermore, behavioral disturbances resulted in relational problems and the termination of relationships regardless of severity of TBI. One in ten of the caregivers received support for dealing with the limitations of the patients.

One in four patients showed severe behavioral disturbances. Most mTBI patients suffered from irritability (82%), anger (49%), and disinhibition (33%) as most prominent characteristics. Moderate-to-severe TBI patients experienced significantly more disinhibition (55%), and significantly less irritation and/or agitation (65%) than patients with mTBI. The prevalence of different types of behavioral disturbances we found, are in line with findings of an earlier study (32). Others however, reported more irritability in severe TBI than in mTBI (7), but summarized only presence of behavioral disturbances without making a distinction between several subtypes of behavior as we did in the current study. A previous study showed that 69% of patients with mTBI resumed work and 44% of mod/sevTBI patients (33). Interestingly in the current study a lower percentage of RTW for mTBI was found, suggesting that the mere presence of behavioral disturbances interferes with RTW and not the severity of these behavioral disturbances. In particular the presence of deficits in judgment and decision-making increased the risk of not resuming work ten-fold. In contrast to RTW, behavioral disturbances did not have a large impact on functional outcome, since in mTBI 96%and in mod/sev TBI 76% showed an favorable outcome. These findings might be influenced by the ceiling effect of the GOSE in mTBI. We chose to dichotomize outcome scores to compare mild and mod/sev TBI patients while mTBI patients mostly score in the upper end with GOSE scores of 7 or 8. Next to this, the return-to-work items of the GOSE are not fully aligned with the separate RTW score we used, resulting in patients scoring "favorable" outcome on the GOSE but "unfavorable" on the RTW score.

The results suggest that behavioral disturbances also have an impact on social life and relations. Almost 15% of patients had relational problems and 40% of the relations were ended. This was in line with a study that also showed a comparable number of received supportive care in 8–20% of spouses (34). No significant difference existed between the support received by caregivers in mTBI and mod/sevTBI. The percentages of relational problems and ended relationships we found might even have been higher, as not all patients have reported these problems specifically or have been asked about this at the outpatient visit. On the other hand, relational problems may have existed before sustaining a TBI. Nevertheless, our findings underline the awareness of the impact of behavioral disturbances after TBI and the necessity of long-term care for both patients and caregivers.

When evaluating the complete pathway of care of all TBI patients with behavioral disturbances in this study, almost all patients returned home despite the fact that one in four patients had serious behavioral disturbances. More than half of the patients were participating in a rehabilitation program within the first six months after injury. A favorable outcome was found

in 54% of patients within a rehabilitation program compared to 47% in patients without active rehabilitation; with RTW in 60 and 61% respectively. Studies regarding this issue are very limited, because previous studies have focused on the pathways of care in all TBI patients and not specifically on TBI patients with behavioral disturbances (22, 35). In our cohort, only a small percentage of the patients (5%) was temporarily admitted to a psychiatric institution. In the subacute phase after injury these patients did not fit criteria for physical and/or cognitive rehabilitation and were (temporarily) admitted to a nursing home. Ultimately, few patients stayed permanently in a nursing home: in total one in ten of patients with mod/sevTBI and only two patients with mTBI, the latter may also have been related to their age (respectively 78 and 88 years old). Compared to a previous study (22), more patients stayed permanently in a nursing home. This finding suggests that patients end up more often in a nursing home in the long term when behavioral disturbances are present, as in the aforementioned study only 67% patients had behavioral impairments.

We also aimed to find associations of different demographic, clinical, and radiological characteristics with behavioral disturbances. Pre-injury mental health problems and substance abuse in mTBI patients were significantly associated with behavioral disturbances, but this was, noticeably, not found in the mod/sevTBI category. It is possible that this last group is so severely impaired that the presence of pre-injury mental health problems/substance abuse is less relevant for definitive outcome in contrast to the traumatic brain injury itself. In contrast to previous studies (17, 18, 36), we did not find any association between structural frontal and/or temporal traumatic brain lesions and the presence of behavioral disturbances or overall outcome. This could be explained by the fact that we only analyzed a preselected patient group with behavioral disturbances and that half of these patients had mild TBI in which no relation is present between localization of lesions and behavioral disturbances. Furthermore, we analyzed associations with behavioral disturbances in general and not with specific behavioral characterizes such as aggression or apathy, which was more common in previous studies (18, 19, 37).

Study Limitations

Several limitations have to be addressed. First, data were collected and interpreted retrospectively using information from our database and the patient charts which resulted in missing and/or incomplete data. Not always complete information was found on the caregivers. Therefore caregiver burden might have been underrated in this cohort. Outcome has been determined at the final stage of the rehabilitation, which occurs at a different moment depending on injury severity. mTBI patients mostly reached their final stage after 6 months, while mod/sevTBI patients mostly reach this final stage one year after injury. Nonetheless, these time intervals are regarded as appropriate to measure a relative stable outcome in all studies on TBI.

CONCLUSIONS

Our study shows a high prevalence of serious behavioral disturbances in patients with various severities of TBI. Half of the patients were not able to return to work in both severity categories suggesting that the presence of behavioral disturbances and not the mere severity influences work resumption. Almost all patients returned home with impact on social life and caregivers resulting in relational problems and the need of support for one in five caregivers. Our findings warrant further research focusing on the impact of behavioral disturbances on work resumption and social life, and the provision of early and appropriate care including the support for caregivers.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical ethical committee university medical center Groningen. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

MT drafted the manuscript and performed the acquisition and analysis of the data. BJ contributed to the analysis and interpretation of data. MS and JS revised the work critically and interpreted the data. JN contributed to the design of the study and interpretation of data. All authors provide approval for publication of the content and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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