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ORIGINAL ARTICLE

The role of early posttraumatic neuropsychological outcomes in the appearance of latter psychiatric disorders in adults with brain trauma

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ABSTRACT

Background: The objective was to determine the predictors of posttraumatic psychiatric disorders (PTPD) during the first 6 months following traumatic brain injury (TBI) focusing on neuroimaging, clinical and neuropsychological appraisements during acute and discharge phase of TBI.

Materials and Methods: We designed a prospective, longitudinal study in which 150 eligible TBI patients were entered. Postresuscitation brain injury severity and discharged functional outcome were evaluated by standard clinical scales. First neuroimaging was done at a maximum of 24 h after head trauma. Early posttraumatic (PT) neuropsychological outcomes were assessed using Persian neuropsychological tasks at discharge. The standardized psychiatric assessments were carefully implemented 6 months postinjury. A total of 133 patients returned for follow-up assessment at 6 months. They were divided into two groups according to the presence of PTPD.

Results: Apparently, aggression was the most prevalent type of PTPD (31.48%). There was no significant difference between groups regarding functional outcome at discharge. Diffuse axonal injury (12.96%) and hemorrhages (40.74%) within the cortex (42.59%) and sub-cortex (33.33) significantly occurred more prevalent in PTPD group than non-PTPD ones. Primary postresuscitation TBI severity, early PT lingual deficit and subcortical lesion on first scan were able to predict PTPD at 6 months follow-up.

Conclusion: Almost certainly, the expansive dissociation risk of cortical and subcortical pathways related to linguistic deficits due to severe intracranial lesions over a period of time can augment possibility of subsequent conscious cognitive-emotional processing deficit, which probably contributes to latter PTPD. Hence, early combined therapeutic supplies including neuroprotective pharmacotherapy and neurofeedback for neural function reorganization can dampen the lesion expansion and latter PTPD.

Key words: Brain injury severity, brain lesions, neuroimaging, posttraumatic lingual deficits

Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in individuals less than 45 years.[1] It is a major cause of deaths following accidents; it especially involves young people and is also a major cause of handicap and morbidity among the survivors.[2] Of all injuries, TBI particularly affects different domains of person's health.[3,4] It is indeed beheld that after TBI, there are dysfunctions in neuropsychological aspects, which have a negative effect on personal and social life.[5] Posttraumatic (PT) neuropsychological dysfunctions are also known as more common sequela post-TBI.[6] Frontal lobe executive dysfunctions, linguistic and memory deficits are the most important neuropsychological outcomes following TBI.[7,8] The intact processing of the memorial, lingual and executive domains were supported by normal functions of brain parts involving the hippocampus, prefrontal cortex (PFC), cingulate gyrus and perisylvian area.[5,9,10] Empirical models in TBI showed that the hippocampus is sensitive to the acute

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apoptotic event.[11] This part of the temporal lobe is engaged for long-term potentiation, which is supposed to be the physiological basis for memory formation and consolidation.[12] In prior studies, greater emphasis has been put on disruption of the prefrontal executive functions including initiation, goal setting, planning, and self-monitoring, as factors in personality and social problems.[13] The recognized linguistic deficits after TBI massively portray the profile of fluent aphasia.[14] It is cleared that linguistic processing deficit after TBI reflected to prefrontal executive dysfunctions and declarative memory deficit, which is a remarkable deficit in TBI and involved PFC, limbic system, hippocampus, and mediodorsal thalamic nucleus functions.[15] Posttraumatic psychiatric disorder (PTPD) is one of the consequences of TBI that the incidence of its various types particularly depression, anxiety and personality changes were reported in many studies.[16-18] Preceding researches have been recorded that anterior cingulate cortex (ACC) lesion is related to the development of mood disorders. ACC is taken into account as the portion of the limbic lobe. Accordingly, it is obvious that ACC lesion after TBI can imperil motivational, emotional and feeling aspects of behavior.[10] In some patients with PT lingual deficit who have given frontal lesion, becoming depress when they become aware of their difficulties.[5] Whelan-Goodinson *et al*. also found a strong relationship between depression after trauma and outcome of TBI.[16-19] Although some authors have claimed that factors such as preinjury psychiatric and education status, gender, age were the high-risk factors of PTPD,[17,20,21] it is crucial to clarify the role of early PT neuropsychological outcomes and injury-related factors including severity, side, type and location of brain injury in this issue. In addition, available evidence represented the powerful association of early psychiatric disorders with latter cognitive and memory deficits in non-TBI population.[22] Hence, we were interested to detect the inverse of this relationship; will early memory, and other neuropsychological deficits inform future PTPD appearance. We also wanted to determine the strong predictors of PTPD in TBI victims during first 6 months after injury. In order to do so, this paper accentuates on evaluating clinical, neuropsychological and neuroimaging outcomes during acute and discharge phase of TBI and comparison of them between PTPD and non-PTPD patients.

Materials and Methods

Participants

A prospective longitudinal design was taken to study TBI adults who were presented to neurosurgery ward of hospital following TBI. A total of 150 patients aged 18–65 years consecutively participated in the ongoing study. Inclusion criteria were conscious survivors at the time of testing and intracranial damages on neuroimaging findings during the initial hospitalization. Patients with preinjury psychiatric disorders and neuropsychological dysfunctions, prior TBI and neurological diseases, mental retardate, and drug abuse history were excluded. None of the included subjects were not noticed psychiatric disorders during discharge phase assessments. Samples were separated to groups with (mean age: 34.7 ± 10.68, mean Glasgow coma score [GCS]: 9.66 ± 2.18) and without (mean age: 35.15 ± 9.94, mean GCS: 9.12 ± 2.55) PTPD at 6 months after TBI. Demographic, clinical and neuroimaging data of patients were recorded in an individual questionnaire. We also divided all TBI patients in five groups respecting TBI type including hematoma, edema, contusion, pneumocephalus, and diffuse axonal injury (DAI), as well as five groups in respect to locus of the lesion inclusive cortex, sub-cortex, brain stem, meninges and ventricles. Thus, we assay neuropsychological and psychiatric outcomes in these groups.

Instruments and procedure

Pathology of the brain was diagnosed using the neuroimaging technique at a maximum of 24 h after head trauma. Type, locus and side of lesion on scans were interpreted by a neuroradiologist unaware of neuropsychological outcomes. The findings were entered on a code sheet that specified the side, anatomic locus including cortex, sub-cortex, meninges and ventricles, as well as intracranial pathology including pneumocephalus, contusion, edema, DAI and intracranial hemorrhages of each focal abnormal intensity. In each patient, among multiple lesions, the most intense and wide site was considered as analyzable lesion site. The severity of TBI was ranked on the basis of the primary postresuscitation GCS. In existing study, severe, moderate and mild TBI were respectively determined by the score of 8 or less, 9–12 and 13–15 on the GCS.[23] Functional outcome was graded by Glasgow outcome scale (GOS)[23] at discharge. History of psychiatric disorders in patient's first-degree relative was explored by research assistants who had been train before.[24] Neuropsychological outcomes were measured by a set of tasks evaluate the lingual, perceptual, memorial and executive functions. PT lingual dysfunction was diagnosed using Persian aphasia test (PAT)[25] by a speech and language pathologist regarding the linguistic profile of patients in PAT, as previously described.[26] Verbal memory and visual memory were explored using the revised Persian version of Wechsler Adult Memory Scale.[27] In order to assess the perceptual dysfunction of all sensory modalities involving visual and auditory, as well as tactile, we applied the direct observation method and providing a set of tasks and predefined commands for patients in a semi-structured evaluation. The current study utilized a widely used measure of executive function, verbal fluency, which depends on self-initiated retrieval and cognitive set shifting. Verbal fluency tasks involve asking patient to generate as many words as possible in 1-min beginning with a specific phoneme such as /s/,/p/called phonological fluency task and pertaining to a specific category such as animals, fruits, flowers, that is, semantic fluency task, as well as alternating fluency task,

which in the participant would be asked to alternate between generating words beginning with "S" and items of clothing. For each fluency condition, the dependent measure was the total number of correct responses then the score was transformed to the percentage. Whole neuropsychological examinations were done during discharge phase; length of time of postinjury at which participants were tested synchronically with the length of hospitalization was averagely 1-week. A psychiatrist was screened subjects with PTPD according to diagnostic criteria in Diagnostic and Statistical Manual of Mental Disorder-IV-TR utilizing a structured clinical interview via a clinical checklist[28] at 6 months after injury.

Statistical analyses

By using SPSS 16.0 IBM (international Business Machines) company, a parametric *t*-test was utilized to scrutinize the significant difference of quantitative variables between patients with and without PTPD. For determining the predictors of PTPD 6 months after injury onset in the multivariate analysis; we applied multiple logistic regression by backward method. Parametric ANOVA statistical test and Scheffe *post-hoc* test were accomplished to compare the quantitative variables among five groups that divided respecting TBI types, as well as lesion locus. Chi-square test was used to survey the significant difference of qualitative variables between studied groups. Hypothesis test was two-tailed, and the significance level was considered 0.05.

Results

There was 11.3% dropout of initial sampling. 17 patients discontinued this research, 4 people due to death and 13 ones because of unwillingness. Analyses were carried out for 133 participants who returned for follow-up assessments at 6 months after injury. Figure 1 illustrates the distribution of PTPD types in participants of this study during first 6 months postinjury. Apparently, aggression was the most prevalent type of PTPD (31.48%). The percentage of patients who faced Apathy at 6 months follow-up was dramatically 25.92%. In individuals with latter PTPD, depression (20.37%) and posttraumatic stress disorder (PTSD) (16.66%) were observed

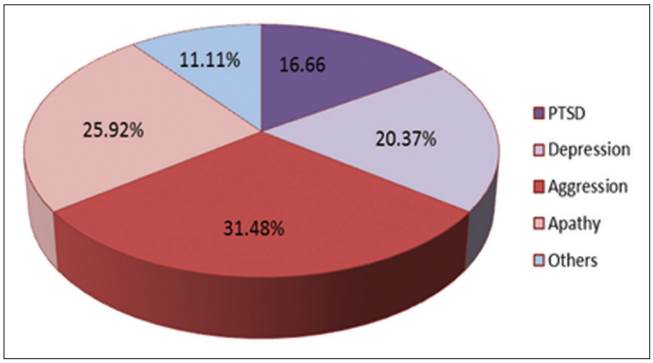

Figure 1: Distribution of posttraumatic psychiatric disorder types in traumatic brain injury adults at 6 months after injury

6 months following TBI. Almost 11% of PTPD cases exhibited other types of PTPD including psychotic syndrome (1.85%), obsessive-compulsive disorder (OCD) (1.85%), generalized anxiety disorder (7.4%). Sexual (9.25%) and sleep (1.85%) disorders were also reported as medical conditions co-occurred to aggression and depression respectively. According to Table 1, results of univariate analysis indicated that there was a significant association between latter PTPD and the followings; lesion type ($P < 0.012$), lesion site ($P < 0.001$) and postresuscitation TBI severity ($P < 0.004$). Neuroimaging results in PTPD patients predominantly displayed intracranial lesions in cortex (42.59%) and sub-cortex (33.33%), whereas meninges (69.62%) were prevalently injured in patients without PTPD. In PTPD group, hematoma (40.74%) and DAI (17.96%) were significantly more common lesion types than non-PTPD ones. Based on primary postresuscitation GCS, severe TBI category was signalized significantly in the PTPD versus the non-PTPD group. No significant association was witnessed between latter PTPD incidence and age ($P < 0.802$), gender ($P < 0.913$), education status ($P < 0.543$), etiology of TBI ($P < 0.711$). Moreover, functional outcome at discharge ($P < 0.493$), lesion side ($P < 0.999$) and family psychiatric history ($P < 0.234$) were not significantly related to latter PTPD occurrence in the first 6 months after injury. More details are represented in Table 1. Tables 2 and 3 illustrate the results of statistical analysis of PT neuropsychological and psychiatric outcomes in patients with several TBI types and locations. According to theses tables were revealed that several TBI groups were significantly different in respect to Executive function ($P < 0.002$), verbal memory ($P < 0.01$), PT lingual dysfunction ($P < 0.03$) and PTPD ($P < 0.02$). Scheffe *post-hoc* test demonstrated that executive function score was significantly different between DAI group and other ones ($P < 0.001$), as well as between Pneumocephalus and other ones ($P < 0.001$). Hematoma ($P < 0.002$) and DAI ($P < 0.001$) groups significantly performed verbal memory task poorer than Edema, contusion, and Pneumocephalus. There was a significant difference among TBI types groups regarding the PT lingual dysfunction ($P < 0.03$) and PTPD ($P < 0.02$). On the other hand, all DAI patients demonstrated PT lingual dysfunctions and psychiatric disorders. Patients suffered pneumocephalus had the lowest percentage of PT lingual dysfunctions and PTPD among TBI types groups. It was also revealed that TBI patients with several lesion locations indicated significant difference in terms of the executive functions ($P < 0.002$), verbal memory ($P < 0.01$), PT lingual dysfunction ($P < 0.003$) and PTPD ($P < 0.002$). *Post-hoc* analysis results signified that patients with meninges lesion performed executive functions task significantly better than patients with cortical ($P < 0.004$), subcortical ($P < 0.004$) and brain stem ($P < 0.002$) lesions. TBI patients with impaired ventricles acquired higher executive functions score rather than cortical ($P < 0.003$), subcortical ($P < 0.002$) and

Table 1: Demographic and injury characteristics of subjects according to PTPD appearance

Variables	PTPD group (*n*=54)	Non-PTPD group (*n*=79)	*P*	All patients (*n*=133)
Age at injury, mean (SD)	34.7 (10.68)	35.15 (9.94)	NS	33.5 (11.2)
Formal education, mean (SD)	8.63 (3.1)	9.25 (2.56)	NS	9.81 (2.31)
Gender, *n* (%)				
Male	40 (74.07)	60 (75.94)	NS	100 (75.18)
Etiology, *n* (%)				
Accident	43 (79.62)	54 (68.35)	NS	97 (72.93)
Fall	9 (16.66)	18 (22.78)		27 (20.3)
Others	2 (3.7)	7 (8.86)		9 (6.76)
Family psychiatric history, *n* (%)				
Yes	4 (7.4)	5 (6.32)	NS	9 (6.76)
No	50 (92.59)	74 (93.67)		124 (93.23)
TBI severity, *n* (%)				
Severe	23 (42.59)	12 (15.18)	0.004	35 (26.31)
Moderate	21 (38.88)	31 (39.24)		52 (39.09)
Mild	10 (18.51)	36 (45.56)		46 (34.58)
GOS grade at discharge, *n* (%)				
Good recovery	26 (48.14)	39 (49.36)	NS	65 (48.87)
Moderate disability	23 (42.59)	30 (37.94)		53 (33.84)
Severe disability	5 (9.25)	10 (12.65)		15 (11.27)
Brain lesion type, *n* (%)				
Hematoma	22 (40.74)	25 (31.64)	0.012	47 (35.33)
Contusion	12 (22.22)	23 (29.11)		35 (26.31)
Edema	10 (18.51)	16 (20.25)		26 (19.54)
Pneumocephalus	3 (5.55)	15 (18.98)		18 (13.53)
DAI	7 (12.96)	-		7 (5.26)
Brain lesion locus, *n* (%)				
Cortex	23 (42.59)	8 (10.12)	0.001	31 (23.30)
Sub-cortex	18 (33.33)	-		18 (13.53)
Meninges	7 (12.96)	55 (69.62)		62 (46.61)
Ventricles	2 (3.70)	9 (11.39)		11 (8.27)
Brain stem	4 (7.4)	7 (8.86)		11 (8.27)
Damaged side, *n* (%)				
Right	26 (48.14)	41 (51.89)	NS	67 (50.37)
Left	21 (38.88)	27 (34.17)		48 (36.09)
Bilateral	7 (12.96)	11 (13.92)		18 (13.53)

DAI – Diffuse axonal injury; PTPD – Posttraumatic psychiatric disorders; TBI – Traumatic brain injury; SE – Standard error; OR – Odds ratio; CI – Confidence interval; SD – Standard deviation; GOS – Glasgow outcome scale; NS – Not significant

Table 2: PT neuropsychological and psychiatric outcomes in all patients respecting TBI typs

Outcomes	All patients (*n*=133)					*P*
	Hematoma (*n*=47)	Contusion (*n*=35)	Pneumocephalus (*n*=18)	Edema (*n*=26)	DAI (*n*=7)	
Executive function score, mean (SD)	37.8 (10.4)	48.9 (10.5)	78.18 (11.28)	44.9 (10.6)	22.7 (9.9)	0.002
Visual memory score, mean (SD)	9.92 (2.03)	10.57 (2.2)	13.46 (3.19)	13 (3.25)	10.3 (2.4)	NS
Verbal memory score, mean (SD)	14.93 (3.2)	25.34 (3.9)	24 (4.6)	23.83 (3.1)	13.79 (3)	0.01
Lingual dysfunction, *n* (%)	22 (46.80)	16 (45.71)	2 (11.11)	8 (30.76)	7 (100)	0.03
Perceptual dysfunction, *n* (%)	5 (10.63)	3 (8.57)	2 (11.11)	2 (7.69)	1 (14.28)	NS
PT psychiatric disorders, *n* (%)	22 (46.8)	12 (34.28)	3 (16.66)	10 (38.46)	7 (100)	0.02

DAI – Diffuse axonal injury; TBI – Traumatic brain injury; PT – Posttraumatic; SD – Standard deviation; NS – Not significant

brain stem ($P < 0.002$) lesions groups. Patients are having cortical lesions significantly exhibited poor performance in the verbal memory task versus patients with ventricle ($P < 0.02$), meninges ($P < 0.001$) and brain stem ($P < 0.04$) lesions. Verbal memory score in subcortical lesion group was significantly lower than subjects with ventricle ($P < 0.01$), meninges ($P < 0.001$) and brain stem ($P < 0.03$) lesions. Moreover, it was discovered that appearance probability of

PT lingual dysfunction ($P < 0.003$) and PTPD ($P < 0.002$) in patients with cortical and subcortical lesions was more than other ones. The results of statistical analyses to explore the association between latter PTPD appearance and early PT neuropsychological outcomes were summed in Table 4, highlighting the insignificant difference between TBI patients with PTPD and without PTPD in terms of the visual memory function ($P < 0.201$) and presence of perceptual dysfunction ($P < 0.097$) at discharge. Two groups were performed significantly different in verbal memory ($P < 0.025$) and executive functions ($P < 0.005$) tasks. In other words, PTPD group obtained lower scores for the executive function, verbal memory tasks than non-PTPD group. Similarly, subjects who had early PT lingual dysfunction were also significantly more likely at risk of the latter PTPD. We entered all above significant variables ($P < 0.1$) in the multiple logistic regression [Table 5]. In the final modeling processing step, postresuscitation TBI severity and exist of early PT lingual dysfunction at discharge, as well as subcortical lesion on scan at first 24 h after injury were the variables, which remained in the final model and hence we can consider them as predictors of PTPD 6 months after TBI onset. Namely, brain injury severity was the first powerful significant predictor of latter PTPD (odds ratio [OR] = 0.54; confidence interval [CI] 95% = 0.09–1.03). It was followed by early PT lingual dysfunction as second (OR = 0.71; CI 95% = 0.1–1.8) and sub-cortex lesion as third (OR = 0.92; CI 95% = 0.57–1.95) strong significant predictors to anticipate PTPD at 6 months after TBI. PTPD was not predicted by other variables included in the regression model.

Discussion

As a result of this study, we absolutely announced that the more the severity of TBI, the more the possibility of PTPD would be. Thus, the primary care can reduce the risk of latter PTPD in persons bearing severe TBI. In subsequence of brain trauma, some functional, structural and biochemical changes in central nervous system may also influence on cognitive, emotional and behavioral processing and took part in the mood disorders[29] and include cell death, reduction in the size of some cortical regions, hypoactivity or hyperactivity of some brain regions, diminished efficiency in neural networks and disturbance of the neurotransmitters balance. Apparently, creation of a sequence of neurobiological events posttrauma such as inflammation, ischemia, excitotoxicity, apoptosis and gliosis, which in turn leads to secondary short and long-term neuronal impairments[30] accompanied by behavioral and emotional alterations and occurs more seriously in severe brain injury.[31] These secondary insults initiated at the moment of injury and continued at future days. Since, widespread delayed nonmechanical damages consecutively befall and are more sensitive to early therapeutic interventions, it is exactly postulated that proper therapeutic supplies can keep from both progression of deleterious disturbed biological processes in the lesion surrounding tissue that called penumbra and deterioration of the brain functions. We found no significant difference between groups respecting the functional outcome according to GOS. Thus, GOS is a sensitive tool to detect the physical complications[32] and is not intrinsically able to assess the mental status which versus physical status probably associated with the psychiatric disorder compared. Surprisingly, none of the individual variables such as age at injury, education status, gender and family psychiatric history were associated with latter PTPD. One possible explanation is that PTPD directly arise from likely prolonged dissociation of synaptic connections in functional brain circuits corresponding with psychiatric components.[30] Hence, a meaningful association of PTPD with injury variables is largely expected, rather than individual variables. Results of our study reflected that patients with latter PTPD represented DAI and hemorrhage within cortex and sub-cortex in their radiological reports significantly more than other intracranial lesions. Such harms preferably related to cognitive-emotional process impairment. Cognitive aspect of the emotional response was controlled by a neural path which is initiated from the central nucleus of the amygdala and projected to the medial dorsal nucleus of the thalamus, ACC and PFC. Based on Maclean's theory, the hippocampus is the part of the cortex that located on the medial temporal lobe where the external world converged with the internal world and played an important role in the conscious feelings and behaviors.[10] Since, the hippocampus is a vulnerable anatomic area after TBI, impairment in hippocampal morphological and functioning or its linked pathways can be bring about the disruption in the integration of cortical and subcortical information related to emotional stimuli. We also realized that early PT lingual dysfunction predicted latter PTPD at 6 months postinjury. It is important to mention that linguistic processing depends on explicit memory that supported by the hippocampus and PFC and circuits related to. Previous clinical studies discovered that linguistic impairment proceeding TBI had a cognitive-communication nature and mostly due to disruption of the prefrontal lobe executive functions and declarative memory. In addition, Executive function is closely linked to the cortical-subcortical circuits of the frontal lobe and plays a critical role in comprehension and production of a message in linguistic macrostructures. Results of functional magnetic resonance imaging (fMRI) studies during implementing verbal fluency test to assess the executive function in healthy individuals showed the activity of bilateral posterior-lateral prefrontal, cingulate gyrus and inferior frontal gyri.[33] Accordingly, intact lingual function depends on healthy function of these cortical and subcortical pathways.[5] In general, the current research manifested that PTPD group significantly performed poorer than non-PTPD ones in both executive function and verbal memory tasks. Two groups had also a significant difference regarding the presence of early PT lingual deficits. Thereupon, affected brain

Table 3: PT neuropsychological and psychiatric outcomes in all patients respecting TBI locations

Outcomes	All patients (*n*=133)					*P*
	Cortex (*n*=31)	Sub-cortex (*n*=18)	Meninges (*n*=62)	Ventricles (*n*=11)	Brain stem (*n*=11)	
Executive function score, mean (SD)	19.44 (9.9)	21.06 (10.11)	59.19 (10.89)	68.3 (11.2)	25.6 (10.33)	0.002
Visual memory score, mean (SD)	9.5 (2.75)	10.18 (2.45)	13.74 (2.3)	13.9 (2.11)	12.18 (2.57)	NS
Verbal memory score, mean (SD)	11.49 (3.5)	12.67 (3.17)	19.3 (2.83)	24.8 (2.09)	22.6 (3.41)	0.01
Lingual dysfunction, *n* (%)	25 (80.64)	13 (72.22)	12 (19.32)	2 (18.18)	3 (27.27)	0.003
Perceptual dysfunction, *n* (%)	4 (12.9)	2 (11.11)	5 (6.45)	1 (9.9)	1 (9.9)	NS
PT psychiatric disorders, *n* (%)	27 (87.09)	14 (77.77)	6 (9.67)	2 (18.18)	3 (27.27)	0.002

TBI – Traumatic brain injury; PT – Posttraumatic; SD – Standard deviation; NS – Not significant

Table 4: Early neuropsychological outcomes in PTPD and non-PTPD groups

PT neuropsychological outcome	All TBI patients		*P*
	PTPD group (*n*=54)	NonPTPD group TBI (*n*=79)	
Executive function score, mean (SD)	23.92 (10.05)	69.07 (11.32)	0.005
Visual memory score, mean (SD)	10.08 (2.62)	11.67 (2.81)	NS
Verbal memory score, mean (SD)	17.43 (3.03)	23.29 (4.11)	0.042
Lingual dysfunction, *n* (%)			
Yes	37 (68.51)	18 (22.78)	0.001
No	17 (31.48)	61 (77.21)	
Perceptual dysfunction, *n* (%)			
Yes	5 (9.25)	8 (10.12)	NS
No	49 (90.74)	71 (89.87)	

PTPD – Posttraumatic psychiatric disorders; TBI – Traumatic brain injury; PT – Posttraumatic; SD – Standard deviation; NS – Not significant

Table 5: Final step of multiple logistic regression model to predict PTPD at 6 months after TBI

Variables	*b*	SE	df	*P*	OR	CI 95%
Step 4						
TBI severity	0.11	1.07	1	0.014	0.54	0.09-1.03
Early PT lingual dysfunction	0.29	0.76	1	0.001	0.71	0.1-1.8
Subcortical lesion	0.35	0.54	1	0.003	0.92	0.57-1.95

PTPD – Posttraumatic psychiatric disorders; TBI – Traumatic brain injury; SE – Standard error; OR – Odds ratio; CI – Confidence interval; PT – Posttraumatic

areas linked to lingual dysfunctions similarly overlap with those already influenced on PTPD. Namely, bilateral PFC and hippocampus are known as crucial parts of the brain related to lingual function[5,10,33] and are engaged for psychiatric function,[34,35] which are also same parts of the brain most susceptible to damage from brain trauma.[30] We identified sub-cortex lesion as a predictive factor of PTPD. We postulate that interruption of connective fibers within brain white matter due to DAI result in disruption of neural interactions related to regulation of psychiatric functions. The findings of ongoing project signify that aggression, apathy and depression were the most prevalent PTPD types respectively. Alleged cortico-thalamic pathways, enclosing, the ACC, accumbens nucleus, ventral pallidum and medial dorsal thalamic nucleus are considered mediators of motivation. Evidently, damages in these circuits generate apathy. PFC and ACC modulate the activity of the amygdala through inhibition. Therefore, appropriate behavior can be run through normal function of these inhibitory projections. In contrast, structural and functional abnormalities in the connections among these regions can rupture the integration of social context information and environmental stimuli in ventral striatum–pallidum that respectively come from ACC and amigdala, so increase trend to impulsive behavior.[34] At a theoretical level, it has been described that hypothalamic pituitary axis (HPA) is involved in depression. Normally, the function of HPA was controlled by intact hippocampus, PFC and amygdala. Damage of each them lead to uncontrolled HPA function, unbalanced adrenocorticotropic hormone and glucocorticoid release and ultimately emersion of depressive signs.[35] Neuroimaging studies using PET or fMRI have demonstrated hyperactive responses of the amygdala-based fear circuitry and decreased activity of medial and orbital PFC regions in humans with PTSD.[36] Physiologically, amygdala is suppressed by inhibitory projections of PFC. We proposed, at a neurobiological viewpoint, that diffuse lesions within subcortical networks of frontal and temporal lobes underpinning language processing develop acute PT lingual deficit and imperil PFC inhibitory effect on amygdala, springing strong emotional memory and propensity to PTSD over time. Undoubtedly, it is obvious that we require further and precise investigations to prove this conclusion. Strict available evidence supported the reduction of serotonin level in aggressive and depressive patients.[34] Some studies emerged concerning the serotonergic imbalance after TBI. Experimental models in TBI clarified disturbance in dopaminergic system[7] that is also considered linked to apathy.[37] The documents implicated the trace of serotonergic and dopaminergic systems in the language processing.[38,39] Clinicians believe that SSRIs and dopamine agonists relatively can improve linguistic deficits.[40] Controversially, about 89% of subjects classified as PTPD were accounted for by aggression, apathy, depression and PTSD that shared the problematic brain areas and neurotransmission systems to PT lingual deficit. Perhaps, this brought about significant association of PT lingual deficit with developing PTPD. One study suggested that subcortical lesion promoted apathy.[41] Thus, it is may be concluded that acute PT lingual deficit and subcortical lesion can exclusively declare the future development of apathy. Confidently, without a precise study, we cannot comment on this issue. More clarifications

conclusively necessitate further investigations. Totally, a few patients showed OCD and psychotic symptoms in present assay. Several studies compatibly pointed to rare emersion of OCD after TBI.[34] Authors disclosed low percentage of TBI patients with PT schizophrenia-like psychosis and concluded that TBI increases the prevalence of schizophrenia over time.[34,42] Researchers reported that positive significant correlation was found between verbal memory and sexual functions.[43] As a limitation in present study, we could not follow our samples for more time after TBI and could not report next neuroimaging results of patients. It is proposed that a research be done in a larger sample size which in effect of PT lingual deficit, serotonin and dopamine level in serum and structural and functional pathology of brain on imaging after acute TBI on the presence of individual types of PTPD were explored. Whether early combined neuroprotective pharmacotherapy and neurofeedbak treatment to restore the neural networks related to PT lingual deficit and prevention of lesion expansion evaluated by serial neuroimaging can reduce possibility of latter PTPD development is also suggested to inquire in the future.

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