Ventromedial prefrontal cortex modulates fatigue after penetrating traumatic brain injury

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ABSTRACT

Background: Fatigue is a common and disabling symptom in neurologic disorders including traumatic penetrating brain injury (PBI). Despite fatigue's prevalence and impact on quality of life, its pathophysiology is not understood. Studies on effort perception in healthy subjects, animal behavioral paradigms, and recent evidence in different clinical populations suggest that ventromedial prefrontal cortex could play a significant role in fatigue pathophysiology in neurologic conditions.

Methods: We enrolled 97 PBI patients and 37 control subjects drawn from the Vietnam Head Injury Study registry. Fatigue was assessed with a self-report questionnaire and a clinician-rated instrument; lesion location and volume were evaluated on CT scans. PBI patients were divided in 3 groups according to lesion location: a nonfrontal lesion group, a ventromedial prefrontal cortex lesion (vmPFC) group, and a dorso/lateral prefrontal cortex (d/IPFC) group. Fatigue scores were compared among the 3 PBI groups and the healthy controls.

Results: Individuals with vmPFC lesions were significantly more fatigued than individuals with d/IPFC lesions, individuals with nonfrontal lesions, and healthy controls, while these 3 latter groups were equally fatigued. VmPFC volume was correlated with fatigue scores, showing that the larger the lesion volume, the higher the fatigue scores.

Conclusions: We demonstrated that ventromedial prefrontal cortex lesion (vmPFC) plays a critical role in penetrating brain injury-related fatigue, providing a rationale to link fatigue to different vmPFC functions such as effort and reward perception. The identification of the anatomic and cognitive basis of fatigue can contribute to developing pathophysiology-based treatments for this disabling symptom. *Neurology*® 2010;74:749-754

GLOSSARY

AAL = Automated Anatomic Labeling; **ANOVA** = analysis of variance; **BDI** = Beck Depression Inventory; **d/IPFC** = dorso/lateral prefrontal cortex; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **NBR** = Neurobehavioral Rating Scale; **NF** = nonfrontal lesion; **PBI** = penetrating brain injury; **ROI** = region of interest; **SCID-I** = Structured Clinical Interview for DSM-IV, Axis I; **VHIS** = Vietnam Head Injury Study; **vmPFC** = ventromedial prefrontal cortex lesion.

Fatigue is a common complaint following penetrating brain injury (PBI), affecting at least a third of PBI patients.¹ Fatigue has been defined as a subjective lack of physical and/or mental energy perceived to interfere with usual and desired activities.² While a host of different mechanisms have been related to fatigue,² recent theories have implicated frontal cortex structures and deep gray matter as the possible neural substrate of fatigue in neurologic disorders.^{2,3} Moreover, recent evidence links medial prefrontal structures to fatigue in neurologic conditions such as multiple sclerosis⁴ as well as to social withdrawal and apathy⁵—i.e., clinical presentations that present with some overlap with the construct of fatigue. Finally, in different experimental paradigms, ventromedial prefrontal cortex

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(vmPFC) territories have been linked with cognitive tasks, such as effort-evaluation, that could help to explain the cognitive underpinnings of fatigue.⁶⁻⁸

In this study, we hypothesized that damage to the vmPFC in PBI patients is associated with fatigue. We studied PBI-related fatigue using the Krupp Fatigue Scale,⁹ a self-report measure of fatigue. The study of fatigue in patients with frontal lobe lesions, however, presents with specific challenges such as the possible lack of disease insight and the difficulty for patients with cognitive disturbances to correctly differentiate between fatigue and other partially overlapping conditions such as apathy (i.e., lack of motivation characterized by diminished goal-oriented behavior and cognition).¹⁰ To address these issues, we decided to use, as a confirmatory measure, a clinician-rated scale (the Neurobehavioral Rating Scale fatigability score)¹¹ as an objective measure of fatigue.

METHODS Subjects. We enrolled 97 PBI patients and 37 controls who did not have PBI from a sample of Vietnam-era war veterans enrolled in the Vietnam Head Injury Study (VHIS).¹² Some characteristics of the VHIS sample make it particularly suitable to study PBI-related fatigue such as the homogeneity of the sample (all male veterans of similar age who sustained brain injury during combat), the availability of preinjury cognitive data, and detailed medical records from long-term follow-up.

Subjects underwent neurologic and psychiatric examinations, neuropsychological testing, and a brain CT scan (an MRI was precluded due to most subjects having retained metal in their brain). All subjects' preinjury characteristics and clinical follow-up data were available from military and Veterans Administration records. All subjects were free of concomitant primary neurologic comorbidities and presented with a medical history negative for chronic pulmonary, cardiovascular, hepatic, and endocrinologic conditions as well as for sleep disorders. Subjects with a pharmacologic history positive for chronic use of drugs known to significantly modulate fatigue^{13,14} including but not limited to CNS stimulants, anxiolytics, hypnotic or antidepressive drugs, and recreational substances were not included in the study.

Anticonvulsant medications were allowed as they are commonly prescribed in this population, and cannot easily be discontinued; however, the effect of anticonvulsive therapy on fatigue level was assessed as a possible confound in the analysis.

Subjects were also free from psychiatric comorbidities assessed through expert clinical evaluation as well as through the Structured Clinical Interview for *DSM-IV*, Axis I (SCID-I),¹⁵ and presented with a Beck Depression Inventory (BDI-II)¹⁶ total score lower than 18. Patients were divided in 3 groups according to the location and the volume of the lesions. Twenty-nine patients did not present any PFC involvement and were thus included in the nonfrontal lesion group. The 68 patients who presented with PFC lesions were divided in 2 groups according to the involvement of the vmPFC: a vmPFC group ($n = 17$) and a d/IPFC group ($n = 51$). All injuries were acquired during

combat and were usually due to low-velocity shrapnel wounds. PBI subjects were screened to have a total lesion volume ≥ 30 mL. All groups were matched on age [$F(3,130) = 0.73$; $p = 0.54$], education [$F(3,130) = 1.50$; $p = 0.22$], BDI-II scores [$F(3,130) = 0.16$; $p = 0.92$], working memory assessed with the N back test¹⁷ [$F(3,130) = 0.93$; $p = 0.42$], and preinjury IQ [$F(3,130) = 1.43$; $p = 0.23$] assessed with the Armed Forces Qualification Test (table).¹²

Fatigue was assessed with the Krupp fatigue scale,⁹ a self-report measure of fatigue that is composed of 9 items rated from 1 to 7, according to a Likert-type scale, where 1 indicates no fatigue-related impairment and 7 indicates severe impairment. Moreover, to control for the possible bias due to reduced insight secondary to frontal lobe damage, subjects were also evaluated using the fatigability subscale of the Neurobehavioral Rating Scale (NBRs).¹¹ The NBRs is multidimensional, clinician-based assessment instrument designed to measure neurobehavioral disturbances in clinical settings and it has been widely used in the assessment of PBI subjects. The NBRs was also used to assess the specificity of our findings to the construct of fatigue. Subjects were thus also tested with 2 other NBRs subscales—i.e., the motor retardation subscale and the emotional withdrawal subscale—that clinically present with a partial overlap with fatigue; all groups were found not to present any significant difference in NBRs motor retardation [$F(3,130) = 0.80$; $p = 0.49$] and NBRs emotional withdrawal scores [$F(3,130) = 1.82$; $p = 0.14$].

Standard protocol approvals, registrations, and patient consents. Before enrollment in the study, all subjects gave informed written consent. All study procedures were approved by our institutional review boards.

CT imaging and lesion identification. Axial noncontrast CT scans were acquired on a GE Light Speed Plus CT scanner in helical mode. Images were reconstructed with an in-plane voxel size of 0.4 mm $\times$ 0.4 mm, overlapping slice thickness of 2.5 mm, and a 1-mm slice interval. Lesion location and volume were determined from CT images by manual tracing using the Analysis of Brain Lesion (ABLE) software¹⁸ contained in MEDx v3.44 (Medical Numerics). A trained neuropsychiatrist (V.R.) performed the tracings, which were then reviewed by an experienced observer (J.G.) who was blind to the results of the clinical evaluations. Each scan was spatially normalized to a CT brain template in MNI space and then the vmPFC was identified in each individual scan. As reported elsewhere,¹⁹ the vmPFC region of interest (ROI) included portions of the following Automated Anatomic Labeling (AAL) atlas²⁰ structures: superior frontal gyrus (medial), superior frontal gyrus (orbital part), superior frontal gyrus (medial orbital), middle frontal gyrus (orbital part), inferior frontal gyrus (orbital part), gyrus rectus, olfactory cortex, anterior cingulate, and paracingulate gyri.

We also assessed each subject's d/IPFC volume loss; the d/IPFC ROI was defined as those areas of PFC superior to the anterior commissure and between 0 and 20 mm left and right from the anterior commissure and included the following AAL structures: medial superior frontal gyrus, dorsolateral superior frontal gyrus, and inferior frontal gyrus, triangular part.²¹

Data analysis. First, we performed a hypothesis-free analysis through a group lesion map approach. This map was composed by the overlay of the individual normalized lesion maps of all PBI patients with a Krupp fatigue score higher than 38, which has been used as cutoff value to identify fatigued patients in clinical populations.²²

Next, according to our hypothesis, we divided the prefrontal PBI veterans into 2 groups: the vmPFC group and the d/IPFC

Table Demographic and clinical data for the control group (n = 37), d/IPFC lesion group (n = 51), vmPFC lesion group (n = 17), and nonfrontal lesion group (n = 29)

Groups	Mean	Standard error
Age		
Controls	59.11	0.62
d/IPFC lesion	58.1	0.39
vmPFC lesion	58.59	1.02
Nonfrontal lesion	58.31	0.47
Total years of education		
Controls	15.54	0.44
d/IPFC lesion	14.72	0.37
vmPFC lesion	13.97	0.77
Nonfrontal lesion	15.04	0.41
Preinjury IQ		
Controls	68.18	4.7
d/IPFC lesion	64.32	3.48
vmPFC lesion	52.53	6.44
Nonfrontal lesion	61.04	5.29
BDI: total score		
Controls	6.03	0.78
d/IPFC lesion	6.6	0.76
vmPFC lesion	6.88	1.25
Nonfrontal lesion	6.17	0.91
N back: total error rate		
Controls	0.81	0.02
d/IPFC lesion	0.82	0.02
vmPFC lesion	0.79	0.02
Nonfrontal lesion	0.84	0.01
Krupp: total score		
Controls	34.14	1.85
d/IPFC lesion	34.8	1.4
vmPFC lesion	42.35	3.4
Nonfrontal lesion	30.48	2.46
NBRS: fatigability		
Controls	1.26	0.13
d/IPFC lesion	1.59	0.14
vmPFC lesion	1.71	0.40
Nonfrontal lesion	0.96	0.18
NBRS: emotional withdrawal		
Controls	1.03	0.03
d/IPFC lesion	1.24	0.08
vmPFC lesion	1.33	0.20
Nonfrontal lesion	1.11	0.06
NBRS: motor retardation		
Controls	1.08	0.06
d/IPFC lesion	1.20	0.08
vmPFC lesion	1.07	0.06
Nonfrontal lesion	1.07	0.05

Abbreviations: BDI = Beck Depression Inventory; d/IPFC = dorso/lateral prefrontal cortex; NBRS = Neurobehavioral Rating Scale; vmPFC = ventromedial prefrontal cortex lesion.

group. A subject was included in the vmPFC group if he or she presented with a PFC lesion that occupied at least 15% of the vmPFC ROI; otherwise, he or she was included in the d/IPFC group. We selected 15% damage as a threshold for inclusion in the vmPFC group because it has been shown that damage to approximately 15% of the vmPFC can be sufficient to yield significant impairments in cortical function.^{19,23}

Fatigue scores and demographic data among the 4 PBI groups were compared using one-way analysis of variance (ANOVA) and post hoc *t* tests. The correlation between fatigue scores and vmPFC lesion volume was assessed with the Pearson test. The effect of BDI scores, d/IPFC volume loss, and working memory deficits assessed with the N back test on the correlation of fatigue scores and vmPFC volume loss was assessed using a partial correlation approach. Finally, to verify the specificity of our findings to fatigue, vmPFC volume loss was correlated with the NBRS motor retardation subscale and the NBRS emotional withdrawal subscale scores. Statistical significance threshold was set at 0.05 after Bonferroni correction for multiple comparisons. All results are reported as mean $\pm$ standard error.

RESULTS Hypothesis-free analysis. In the whole PBI group, 39 out of 97 subjects presented with a Krupp total score higher than 38; the corresponding lesion overlap map is reported in figure 1. The map revealed an overlap of focal damage of vmPFC areas in fatigued subjects.

Hypothesis-driven analysis: vmPFC and fatigue. Krupp fatigue and NBRS fatigability scores for the 4 groups (vmPFC, d/IPFC, nonfrontal, and control groups) are reported in the table and figure 2.

An ANOVA on the Krupp Total Score among the 4 groups revealed a significant group effect [$F(3,130) = 3.75$; $p = 0.013$]. Follow-up post hoc comparisons revealed a significant difference in fatigue scores when comparing the vmPFC lesion group (score: 42.3 ± 3.4 ; $p = 0.01$) with the d/IPFC lesion group (score: 34.8 ± 1.4 ; $p = 0.01$), with the nonfrontal group (score: 30.5 ± 2.5 ; $p = 0.001$), and with the control group (score: 34.1 ± 1.8 ; $p = 0.01$). The other comparisons were not significant.

The ANOVA on the NBRS fatigability subscale scores also revealed a significant group effect [$F(3,130) = 7.5$; $p = 0.001$]. Follow-up post hoc comparisons revealed a significant difference in fatigue scores when comparing the vmPFC lesion group (score: 2.73 ± 0.44 ; $p = 0.001$) with the d/IPFC lesion group (score: 1.59 ± 0.14 ; $p = 0.001$), with the nonfrontal group (score: 1.39 ± 2.5 ; $p = 0.001$), and with the control group (score: 1.26 ± 0.03 ; $p = 0.001$). The other post hoc comparisons were not significant.

Taking into account those PBI subjects with vmPFC damage, the correlation between Krupp Total Scores and vmPFC volume loss (correlation coefficient $r = 0.33$; $p = 0.006$) was significant, as well as the correlation between NBRS fatigability score and vmPFC volume loss (correlation coefficient $r =$

Figure 1 Overlap map of lesioned areas in fatigued penetrating brain injury subjects

The map is shown in MNI space, overlapped on a standard brain template. Note the prevalent involvement of ventromedial prefrontal cortex. Percentages on the right of the map color code represent the fraction of subjects with lesions in the voxel.

0.24; $p = 0.0053$), while there was no significant difference in total volume loss between the vmPFC lesion group and the d/IPFC lesion group (alpha = 0.05; 87.85 ± 11.40 mL vs 72.80 ± 10.40 mL).

The correlation between Krupp Total Scores and vmPFC volume loss remained significant after taking into account BDI scores (correlation coefficient $r = 0.21$; $p = 0.01$), d/IPFC volume loss (correlation coefficient $r = 0.20$; $p = 0.02$), and N back total error rates (correlation coefficient $r = 0.22$; $p = 0.01$) using a partial correlation approach.

The correlation between NBRS fatigability and vmPFC volume loss also remained significant after taking into account BDI scores (correlation coefficient $r = 0.24$; $p = 0.003$), d/IPFC volume loss (correlation coefficient $r = 0.21$; $p = 0.005$), and N back total error rates (correlation coefficient $r = 0.31$; $p = 0.001$) using a partial correlation approach.

The correlations between vmPFC volume loss and the other NBRS measures considered in the study—the NBRS motor retardation subscale scores ($p = 0.16$) and NBRS emotional withdrawal subscale scores ($p = 0.47$)—were not significant.

Finally, we divided all our TBI subjects according to the current use of anticonvulsant drugs, as anticonvulsant use could be related to the perception of fatigue.²⁴ In our TBI cohort, 28 (out of 97) subjects

were using at least one anticonvulsant drug (drugs used included phenytoin, 16 subjects, carbamazepine, 7 subjects, valproic acid, 9 subjects, and lamotrigine, 3 subjects), but we did not find a difference in fatigue scores between treated and untreated subjects (38.8 ± 2.2 vs 33.9 ± 1.5 ; $p = 0.770$).

DISCUSSION The aim of this study was to evaluate the role of vmPFC in PBI-related fatigue. In different clinical populations, fatigue has been linked, albeit inconsistently, with alterations in a host of different brain structures, such as the monoaminergic nuclei,²⁵ the ascending reticular formation,²⁶ and the frontostriatal network.^{2,27} The heterogeneity of these findings could be related to the different patients population studied, the subjectivity of fatigue perception complaint, or the effect of multiple confounding factors such as mood, disease duration, education, and age.

Our hypothesis of a central role for vmPFC areas in fatigue perception was based on the behavioral affinities between fatigue and other clinical conditions such as mood disorders and apathy in which vmPFC dysfunction is thought to play a significant role⁵ as well as on the relationship between medial frontal territories alterations and fatigue in patients with multiple sclerosis.^{16,27}

In our study, the relationship between vmPFC lesions and fatigue was first illustrated by a lesion

Figure 2 Fatigue scores for the 4 experimental groups

Krupp fatigue scale (A) and Neurobehavioral Rating Scale fatigability scores (B) for the control group, dorso/lateral prefrontal cortex (d/IPFC) lesion group, ventromedial prefrontal cortex lesion (vmPFC) lesion group, and nonfrontal (NF) lesion group. The asterisk indicates a significant difference between 2 groups ($\alpha = 0.05$ after correction for multiple comparisons) at the post hoc analysis.

map overlap approach that showed a focal involvement of vmPFC structures in fatigued PBI subjects. Using a hypothesis-driven approach, we then showed more specifically that subjects with vmPFC damage were significantly more fatigued than subjects with nonventromedial prefrontal lesions, subjects with nonfrontal lesions, and controls (all 3 latter groups were equally fatigued). Moreover, we showed a significant correlation between fatigue scores and the volume of the vmPFC lesions, indicating that the larger the lesion volume the higher the fatigue scores.

While our primary fatigue measure was a self-report questionnaire, we also tested our subjects with a clinician-rated scale of fatigability; the analysis of this clinician-rated scale (i.e., the NBRS fatigability subscale) confirmed our observations of a central role for vmPFC in PBI-related fatigue.

Contemporary constructs of fatigue are heterogeneous not only because complaints of fatigue are notoriously subjective, but also because cognitive, neuroendocrine, peripheral, and psychosocial factors might interact to produce different degrees of fatigue perception.² In different neurologic conditions, for example, fatigue has been associated with hypothalamic-pituitary-adrenal axis dysfunction²⁸ and autonomic deficits.²⁹ These observations are consistent with the idea that the vmPFC plays a central role in fatigue percep-

tion: the vmPFC has rich connections with areas involved in neuroendocrine and visceromotor control such as the hypothalamus,³⁰ and is prominently interconnected with the lateral orbitofrontal cortex, which receives inputs from the cortical areas associated with most of the sensory systems, including somatic sensation.³¹ Moreover, the vmPFC plays a significant role in the evaluation and selection of motor and cognitive outputs, codes the incentive value of expected outcomes,⁶ and coordinates with other medial frontal territories in the evaluation of effort-based decision making.^{7,8} The observation of a significant role of vmPFC territories in perception of effort and its subsequent rewards together with our findings of a relationship between vmPFC integrity and fatigue could be instrumental to reframe the current construct of fatigue to include a possible pathophysiologic explanation of this multifaceted symptom, i.e., to link fatigue to these cognitive processes that physiologically encode effort and reward quantifications. More studies are necessary to verify this hypothesis.

Unique characteristics of this study are the homogeneity of the population studied, the availability of preinjury data, and a long clinical follow-up compared to other studies of fatigue perception.^{1,4,9} These factors enabled us to account for the impact of different cognitive, demographic, and psychosocial factors that might play a role in fatigue perception.²

One limitation on the interpretation of our study is its reliance only on male subjects with PBI; further studies are needed to expand these observations to females and subjects with other neurologic disorders. Other limitations of the study include the different numbers of the experimental groups and the possible confounds due to prescription and over-the-counter medications; we tried to reduce the effect of the latter confound, however, through a detailed pharmacologic history. Nevertheless, the consistency of our findings with other recent studies described above^{2,3,4,22} strengthens the validity of the results and suggests that treatments aimed at regulating vmPFC function and reward mechanisms might restore energy to those patients who complain of fatigue following brain damage.

DISCLOSURE

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