

## Evaluating the cognitive consequences of mild traumatic brain injury and concussion by using electrophysiology

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**Object.** Mild traumatic brain injury (MTBI), often referred to as concussion when it occurs in sports, produces persistent cognitive problems in at least 15% of patients. Unfortunately, conventional neuropsychological tests usually yield results within normal limits in this population. The main objective of this event-related potential (ERP) study was to understand brain functioning during the performance of a working memory (WM) task in patients who have sustained an MTBI, mostly due to motor vehicle accident or sports concussion. This study also aimed for a better understanding of the association between brain functioning as measured with ERP, behavioral performance on the WM task, postconcussion symptoms, type of injury (that is, sports concussion vs other types), and time since the injury.

**Methods.** Forty-four patients with MTBI ( $7.6 \pm 8.4$  months postinjury) were tested on a visual WM task with simultaneous recording of ERP, and were compared with 40 control volunteers who were their equivalent for age and sex. Amplitude and latency of frontal (N200 and N350) and parietal (P200 and P300) ERP waves were measured and were compared between groups. Correlation analyses were also performed between ERP characteristics, clinical variables, and behavioral performance.

**Results.** A significant group difference was found for behavioral performance on the WM task, in which the MTBI group had a lower percentage of correct answers than the control group ( $p < 0.05$ ). The patients with MTBI also had smaller amplitudes of both frontal N350 and parietal P300 ERP components when compared with control volunteers ( $p < 0.05$ ). No changes were found for latency of ERP components. Smaller ERP amplitudes were associated with slower reaction times and worse accuracy on the WM task among patients with MTBI ( $p < 0.05$ ). Types of injury (that is, sports concussion vs other mechanisms) were not associated with different ERP characteristics.

**Conclusions.** Abnormal ERP results are observed in patients after MTBI or sports concussion, even for those in the nonacute stage after their injury. Current standard clinical evaluations most often fail to detect cerebral dysfunction after MTBI, even when patients or athletes report symptoms. Clinicians should be aware that patients with MTBI, including sports concussion, probably have underlying mild but persistent cerebral dysfunctions that require further investigation.

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**KEY WORDS** • **concussion** • **mild traumatic brain injury** • **event-related potential** • **working memory** • **electroencephalography**

**M**ILD traumatic brain injury, often referred to as concussion when it occurs in sports, is known to produce persistent cognitive problems in at least 15% of patients.<sup>4,10</sup> Common cognitive complaints include concentration problems, memory deficits, and reduced information-processing speed.<sup>4,9</sup> Among risk fac-

tors associated with chronic symptoms are a history of multiple concussions, increasing age, female sex, pain, litigation, and psychiatric or psychological comorbidities.<sup>11,13,21,29</sup> Unfortunately, conventional neuropsychological tests usually yield results within normal limits for patients with MTBI who report cognitive problems.<sup>5</sup> The cognitive deficits, when present, are subtle, although they may often interfere with activities of daily living, driving, and performance at work, sports, and school.<sup>8,22,35</sup>

In an attempt to elucidate the underlying neurophysiological bases of covert cognitive dysfunctions associated with MTBI, recent studies have used electrophysiology

*Abbreviations used in this paper:* BDI-II = Beck Depression Inventory, 2nd edition; DLPFC = dorsolateral prefrontal cortex; EEG = electroencephalographic; ERP = event-related potential; fMRI = functional MRI; MTBI = mild traumatic brain injury; PCS-R = Post-Concussion Scale-Revised; WM = working memory.

cal and neuroimaging techniques. Functional MRI and ERPs have been found to be among the most sensitive of these techniques (for recent reviews see Gosselin and colleagues<sup>25</sup> and McDonald and colleagues<sup>37</sup>). One advantage of these approaches is that they allow the measurement of brain function during the performance of a cognitive task. In patients with MTBI and in concussed athletes, tasks known to recruit the mid-DLPFC are of particular interest, because this cortical region is reportedly vulnerable to MTBI.<sup>33</sup> Our laboratory has conducted a series of studies using fMRI and the externally ordered task that evaluates the ability to monitor (keeping track) of stimuli in WM. There is excellent evidence that this task recruits specifically the mid-DLPFC.<sup>39,40,42</sup> In our previous studies, we have consistently observed a reduction in the mid-DLPFC activation after MTBI in motor vehicle accident victims as well as in concussed athletes. This reduction has been associated with symptom severity; that is, the more severe the symptoms, the lower the activations observed in the mid-DLPFC.<sup>14–16,23,24</sup>

Only a limited number of studies have used ERP during the performance of a WM task to further refine our understanding of the cognitive sequelae of MTBI. The ERP is a noninvasive method that represents the electrophysiological signal associated with stimulus perception and cognitive processes during a task. This technique assesses the time course of cerebral processes with milliseconds precision. In a recent study, preliminary data on 14 patients with MTBI or concussion showed that the frontal N350 ERP wave associated with WM was abnormal when compared with control volunteers.<sup>23</sup> This anomaly was concurrently associated with reduced fMRI activation in the mid-DLPFC during the performance of the same externally ordered WM task. These results need to be confirmed in a larger sample of patients with different types of injury, for example motor vehicle accident and sports concussion.

### Objectives and Hypothesis

The main objective of the present study was to understand brain functioning during the performance of a WM task that requires monitoring or “keeping track” of stimuli in a larger sample of patients who have sustained an MTBI (mostly due to a motor vehicle accident or sports concussion). To achieve this goal, we compared ERPs from 46 individuals with MTBI to a group of 40 healthy control volunteers. More specifically, we measured amplitude, latency, and scalp distribution of specific ERP components. We hypothesized that the frontal ERP components (N200 and N350) representing WM processes and the parietal ERPs (P200 and P300) underlying attention processes would have smaller amplitudes in patients with MTBI and with concussion than in healthy control volunteers. We expected that no or a limited group difference would emerge from the ERP latency and scalp distribution analyses.

In addition, we aimed for a better understanding of the association between brain functioning, behavioral performance on the WM task, postconcussion symptoms reported by the patients, and time since the injury. We hy-

pothesized that smaller ERP amplitudes would be associated with worse behavioral performance, higher symptom severity, and shorter time since the injury.

## Methods

### Patient Population

Demographic and clinical characteristics of patients with MTBI and controls are presented in Table 1. Forty-four patients with MTBI were recruited from the McGill University Health Centre and the Hôpital du Sacré-Coeur de Montréal, 2 tertiary trauma centers in the Montreal (Canada) area. The inclusion criteria for the MTBI group were as follows: 1) diagnosis of MTBI in the past 36 months; and 2) age between 16 and 60 years. The exclusion criteria were as follows: 1) involvement in litigation; 2) presence or history of neurological and/or psychiatric conditions; 3) substance abuse; and 4) use of drugs known to affect cognition (including benzodiazepines). The MTBI diagnoses were made by a physician according to the following criteria:<sup>7</sup> a Glasgow Coma Scale score of 13–15 and the presence of one or more of the following manifestations: confusion/disorientation, loss of consciousness ( $\leq 30$  minutes), posttraumatic amnesia ( $< 24$  hours), and/or transient neurological abnormalities. None of the participants with MTBI needed a neurosurgical intervention.

Twenty-four of 44 patients had sustained their MTBI in the context of sports, 14 had been involved in a motor vehicle accident, and the remaining patients had been involved in bicycle accidents (2), sustained injuries at work (3), or suffered an assault (1). Among the MTBI group, 14 patients had been included in a previous ERP and fMRI study in our laboratory.<sup>23</sup> The MTBI group was compared with 40 control volunteers who were their equivalent for age and sex. No control participants had a diagnosis or history of neurological and/or psychiatric conditions (including previous TBI and substance abuse) and no one used drugs known to affect cognition. All participants completed the PCS-R<sup>34</sup> and the BDI-II<sup>3</sup> to document symptom severity. The protocol was approved by the hospital research ethics committees (McGill University Health Centre and Hôpital du Sacré-Coeur de Montréal). All participants gave written informed consent before the beginning of the study.

### Data Acquisition

We used the externally ordered WM task adapted for ERP recording (see Gosselin et al.<sup>23</sup> for a detailed description). Briefly, during each trial of this task, 4 abstract images selected randomly from the same set of 5 images were presented successively at the center of the screen. Participants were instructed to monitor which items appeared on each trial, and after a short delay following the sequential presentation of these items, 1 of the 5 stimuli was shown on a test trial and participants had to decide whether the test item was among the 4 previously presented items. Participants responded by pressing a left or right mouse button to indicate their choice of yes or no. In the control condition, during the stimulus presentation phase

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**TABLE 1: Demographic and clinical characteristics of patients with MTBI and controls\***

Variables	MTBI Group (n = 44)	Control Group (n = 40)	p Value
demographic characteristics			
no. F/M	21:23	23:17	NS
age (yrs)	30.3 ± 11.1	28.6 ± 10.5	NS
education (yrs)	13.9 ± 3.3	15.4 ± 2.6	0.02
handedness	40 rt, 4 lt	40 rt, 0 lt	NS
clinical characteristics			
time since MTBI (mos)	7.6 ± 8.4	NA	NA
PCS-R total score	41.1 ± 24.4	7.1 ± 7.3	<0.0001
BDI-II total score	14.8 ± 9.0	4.1 ± 4.6	<0.001

\* Values for age, education, and clinical characteristics are given as the mean ± SD. Abbreviations: NA = not applicable; NS = not significant.

a single image was presented 4 consecutive times. After a delay, 1 of 2 images associated with either a left or a right mouse button press was presented, and participants had to provide the appropriate response. They practiced the WM task extensively to familiarize themselves with the set of images and the experimental procedure before undergoing the ERP session. Stimulus presentation duration was 1000 msec, and the interstimulus interval was also set at 1000 msec to avoid overlap in EEG responses.

### Data Analysis

The EEG data were processed using BrainVision Analyzer software (Brain Products GmbH). First, EEG data were removed from bad channels by visual inspection and rereferenced to the average channel. Additional filters (0.01–50 Hz, 12 dB/octave) were subsequently applied. Those trials in which ocular movement artifacts exceeded ± 70 µV were rejected automatically. Ocular movement artifacts were corrected using BrainVision software, and a 100-msec prestimulus baseline correction was performed. The EEG data were segmented according to each phase (that is, stimulus presentation phase and decision phase) and condition (that is, WM and control conditions), with a 100-msec prestimulus onset baseline. The EEG segments were then averaged for each phase and condition, resulting in 4 average ERP waveforms as follows: 1) stimulus presentation phase in the WM condition; 2) stimulus presentation phase in the control condition; 3) decision phase in the WM condition; and 4) decision phase in the control condition. Amplitude and latency of ERP components were measured relative to the mean of the prestimulus baseline for each averaged ERP waveform.

Latency and amplitude of the N200 and N350 components were measured on the maximal negative peak within the latency window of 180–300 and 300–475 msec, respectively. The P200 and the P300 components were defined as the highest positive peaks occurring within 180–300 and 300–550 msec, respectively. Amplitudes and latencies were averaged across electrode pools to form 6 distinct regions of interest: left anterior (electrodes AF7, F5, F7, F9); median anterior (AFz, Fz, F1, F2); right anterior (AF8, F6, F8, F10); left posterior (P5,

P7, P9, PO7); median posterior (Pz, P1, P2, POz); and right posterior (P6, P8, P10, PO8). The N200 and N350 waves were analyzed only with the anterior electrode pools, whereas the P200 and P300 waves were analyzed with the posterior pooled electrodes.

### Statistical Analysis

To test our first hypothesis, namely that ERP waves will have lower amplitude in the MTBI than in the control group with no or limited changes observed on latency and scalp distribution, a 2-way mixed ANOVA (Group [MTBI vs control] by Region of interest [left, median, right]) was performed on the amplitude and latency for each of the ERP components, for each condition (that is, WM and control conditions) and for each task phase (that is, stimulus presentation and decision phases). The region of interest approach was based on a previous study examining scalp distribution of ERP associated with WM in healthy control volunteers.<sup>1</sup> Pearson correlations were performed to test the association between ERP and other variables: that is, scores on questionnaires; time since MTBI; reaction times; and accuracy. Student *t*-tests were done to compare the influence of types of injury (sports vs other) on ERP variables. Statistical analyses comparing the 2 groups on demographic data, questionnaires, and behavioral variables were conducted using Student *t*-tests. Because tests were performed for 2 different conditions (WM and control conditions), all analyses conducted to address our first hypothesis were considered to be significant at  $p < 0.025$ . The Bonferroni correction was applied to correlation analyses aimed at testing our second hypothesis. Statistical analyses were performed using the software Statistica 10 (StatSoft, Inc.).

## Results

### Symptoms Reported by Patients

Patients with MTBI had significantly higher scores than controls on the PCS-R and the BDI-II (see Table 1), representing higher postconcussive and depression symptoms. Scores on questionnaires, time since injury, and education did not differ according to types of injury;

however, patients with sports concussion were younger than those who had sustained their MTBI in a context other than sports ( $26.1 \pm 8.4$  vs  $35.4 \pm 12.0$  years of age). Exploratory analyses using Student t-tests were also performed to verify gender differences on questionnaire results, and no significant differences were found.

### Behavioral Results

Table 2 shows the reaction times and accuracies for the WM and control conditions of MTBI and control participants. A significant group difference was found for WM accuracy ( $t(82) = -2.30, p = 0.024$ ); the MTBI group endorsed a lower percentage of correct answers than did the control group. No group difference was observed for the control condition accuracy or for reaction times in the WM task, although the control volunteers tended to be faster than patients with MTBI in the performance of the control task ( $t(83) = 1.99, p = 0.05$ ). Demographic and clinical variables (age, sex, education, time since MTBI, type of injury, PCS-R total score, and BDI-II total score) were not associated with reaction times or accuracy in patients with MTBI.

### Event-Related Potentials

Figure 1 presents grand average ERP waveforms for patients with MTBI and controls. Only Group effects or Group by Region interactions are reported in the following section, because Region effects were not among the objectives of this study. Moreover, no Group effects or Group by Region interactions were found for ERP latencies, and only those results observed for amplitudes are reported.

**N200.** No Group effects or Group by Region interactions were found for the N200 amplitude for either the WM or the control conditions.

**N350.** A Group effect was observed for the N350 amplitude in the decision phase for the WM condition ( $F(1, 80) = 6.11, p = 0.016$ ), where patients with MTBI showed smaller amplitude in comparison with controls; this group effect was specific to the WM condition and was not observed for the control condition.

**P200.** No Group effects or Group by Region interactions were found for the P200 amplitude for the WM or the control conditions.

**P300.** A Group effect was observed for the P300 am-

plitude in the decision phase for the WM condition ( $F(1, 80) = 9.33, p < 0.01$ ). As observed with the N350 wave, patients with MTBI had smaller amplitudes for the P300 wave when compared with controls. A trend for a Group by Region interaction was observed for the control condition ( $F(2, 154) = 3.13, p = 0.046$ ), and planned comparisons showed Group effects for the left posterior and median posterior regions ( $p < 0.01$ ); patients with MTBI had lower amplitudes than controls in those areas. No Group effect was found for the right posterior area.

### Association Between Demographic, Clinical, and Behavioral Variables and ERP

To limit the number of statistical tests, Student t-tests and correlations between demographic, clinical, and behavioral variables were performed only with the ERP variables that showed a Group effect or a Group by Region interaction; that is, the N350 and P300 amplitudes. For these analyses the Bonferroni correction was applied because 8 tests had been performed for each independent variable level (reducing the significance threshold from 0.05 to 0.006).

**Clinical Variables.** The time since MTBI was significantly correlated with the N350 amplitude in the WM task for the left anterior region only ( $r = -0.31, p < 0.006$ ); the long delays post-MTBI were associated with higher (more negative) amplitudes. In addition, more severe depression symptoms were found to correlate with lower P300 amplitude for the WM task (median posterior region:  $r = -0.31, p < 0.006$ ). Types of injury (sports concussion vs others) were not associated with ERP characteristics.

**Behavioral Variables.** Behavioral performance on the WM and control conditions correlated with ERP characteristics in patients with MTBI. Slower reaction times for the WM condition were associated with smaller P300 amplitudes (median posterior region:  $r = -0.41, p < 0.006$ ). Worse accuracy in the WM condition tended to be associated with the P300 amplitude (median posterior region:  $r = 0.34, p = 0.04$ ). No significant correlations were found between behavioral performance and ERP characteristics for the control condition.

## Discussion

The aim of our study was to use ERP for further elucidation of the cognitive changes associated with per-

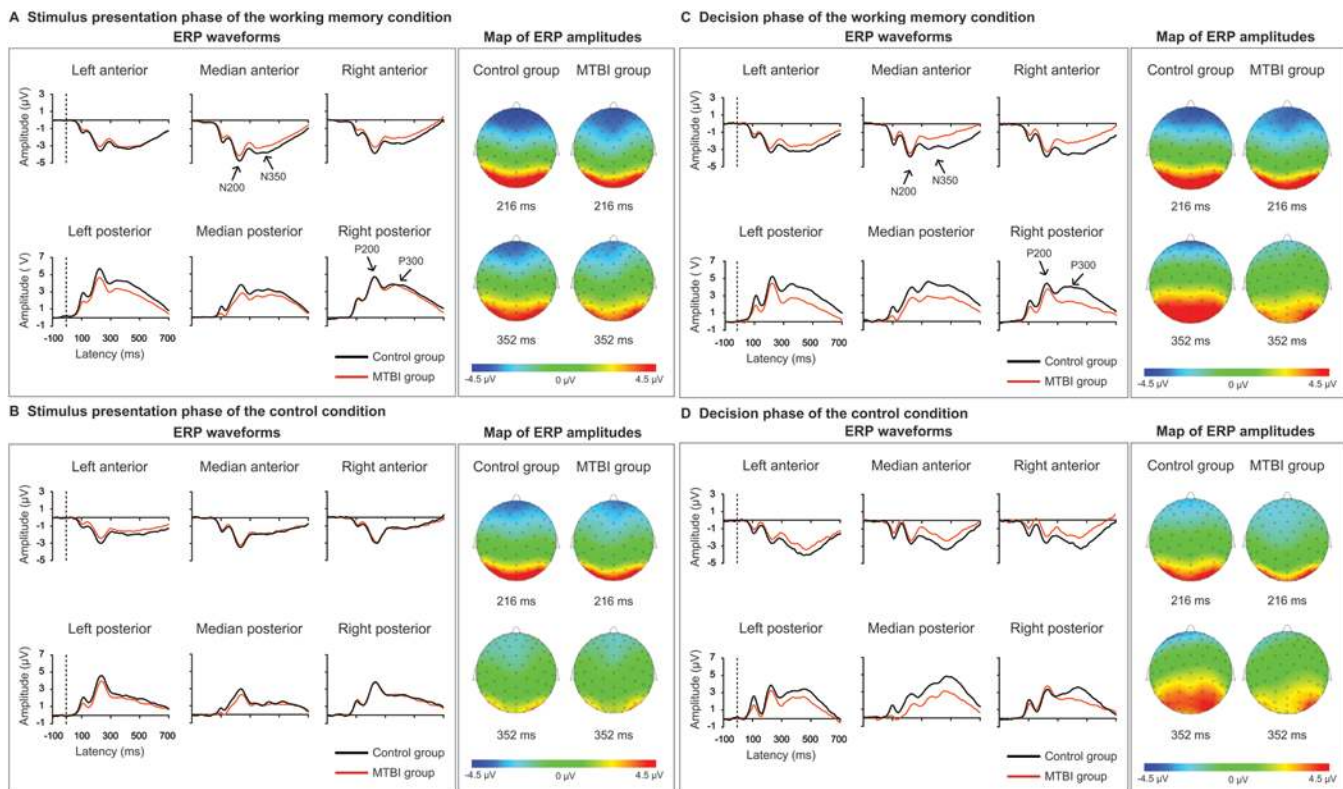
**TABLE 2: Behavioral data observed during ERP studies for patients with MTBI and controls\***

Variables	MTBI Group	Control Group	p Value
WM condition			
reaction time (msec)	1096.0 $\pm$ 348.0	993.5 $\pm$ 281.7	NS
accuracy (%)	83.3 $\pm$ 12.6	88.9 $\pm$ 9.4	0.02
control condition			
reaction time (msec)	786.3 $\pm$ 257.0	693.2 $\pm$ 154.8	NS
accuracy (%)	96.2 $\pm$ 10.9	96.9 $\pm$ 8.2	NS

\* Values are given as the mean  $\pm$  SD.



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**Fig. 1.** Grand averaged ERP waveforms and maps of ERP amplitudes for patients with MTBI and control volunteers. The ERPs were recorded during the stimulus presentation phase of the WM condition (**A**), the stimulus presentation phase of the control condition (**B**), the decision phase of the WM condition (**C**), and the decision phase of the control condition (**D**). *Left-hand panels:* grand averaged ERP waveforms for the control and the MTBI group. The N200 and N350 ERP components appear on anterior electrodes, whereas P200 and P300 ERP components can be observed on posterior electrodes. *Right-hand panels:* maps of ERP amplitudes of the control (left) and MTBI group (right). The ERP amplitudes at 216 msec (ms) following the stimulus presentation are presented on the upper part and the ERP amplitudes at 352 msec are presented on the lower part of these panels. Color scale represents amplitude values from  $-4.5 \mu\text{V}$  to  $4.5 \mu\text{V}$ , with *blue* representing negative ERP components (that is, N200 and N350) and *red* representing positive ERP components (that is, P200 and P300).

formance on a monitoring WM task in a relatively large sample of patients who have sustained an MTBI, including sports concussion. Our results showed that patients with MTBI had smaller amplitudes (or less negative amplitudes) of both the frontal N350 and the parietal P300 ERP components when compared with controls. Individuals with more severe depression symptoms showed greater reduction in P300 amplitudes. Lower ERP amplitudes were also associated with slower reaction times and worse accuracy among patients with MTBI. This study confirms that cognitive changes occur in patients who have sustained MTBI of different causes, including sports concussion. Because no correlation was observed between ERP characteristics and time since MTBI (except for a correlation between the N350 amplitude in the right anterior region), these results suggest that most of these cognitive changes may persist for extended periods after an MTBI.

## Event-Related Potentials, MTBI, and Concussion

Several studies have used electrophysiological techniques, mostly ERP, to identify and understand the cerebral/cognitive consequences of MTBI and sports concussion. These studies have consistently reported reduced amplitudes or delayed latencies of ERP components after

MTBI and sports concussion, particularly for the P300 (which is probably one of the ERP components most sensitive to a general cerebral dysfunction).<sup>43</sup> Surprisingly, abnormal ERP components have been observed not only in the acute stage after MTBI, but also several months and years thereafter.<sup>9,19,23,25,26,31,46</sup> Moreover, abnormal ERP components were found even when concussed athletes did not report symptoms.<sup>23,32,45,46</sup> Taken together, ERP studies have shown that MTBI and sports concussion produce mild but persistent cerebral changes that can be observed even when patients are asymptomatic. Similar conclusions have been reached in several other studies in which different techniques were used, such as transcranial magnetic stimulation,<sup>18–20,44,48</sup> proton MR spectroscopy,<sup>17,47</sup> diffusion tensor imaging,<sup>28,30,38</sup> and voxel-based morphometry.<sup>47</sup> These studies have all reported evidence consistent with long-term neuronal and axonal damage, as well as reduced synaptic plasticity after MTBI or sports concussion. These findings are in contrast to the general assumption that in most patients symptoms and cerebral functioning return to normal after 7–10 days postinjury.<sup>6</sup>

## Working Memory After MTBI and Sports Concussion

Working memory deficits are among the most preva-

lent cognitive deficits following MTBI and sports concussion.<sup>36</sup> Because WM is critical for the successful performance of many high-level cognitive functions, even mild deficits can have a significant impact on general cognitive functioning and on functioning in overall everyday activities. Unfortunately, subtle WM deficits are not easily detectable with the standard neuropsychological tools, because patients with MTBI generally demonstrate results within normal limits. However, in the present study patients with MTBI showed worse accuracy on the WM task than controls. The sensitivity of the externally ordered task designed by Petrides<sup>39</sup> specifically to evaluate the role of the mid-DLPFC in WM is most likely due to the fact that it measures the high-level control process of monitoring information rather than the maintenance of information. A series of studies on lesions and their effects on behavior, and also functional neuroimaging studies, have linked this specific process to the mid-DLPFC.<sup>12,39–42</sup> The integration of such WM tasks into clinical neuropsychological evaluations should be encouraged for better detection of changes in cognitive functioning after MTBI and sports-related concussion. Moreover, WM tasks that specifically recruit the mid-DLPFC, such as the externally ordered WM task, could be useful with other clinical populations such as patients with major depression or schizophrenia, in whom mid-DLPFC dysfunctions have been documented.<sup>2,27</sup>

### Conclusions

This study showed that abnormal ERP results are observed in patients in their postacute and long-term stages after MTBI. Current standard clinical evaluations most often fail to detect cerebral dysfunction after MTBI, even when patients or athletes report symptoms. This lack of sensitivity of current clinical tools and the incongruence between reported symptoms and clinical observations can lead to patient distress, poor management of postconcussive symptoms, and difficulty with the decision to return to play or to work or school. Clinicians should be aware that patients with MTBI or sports concussion probably have underlying mild but persistent cerebral dysfunctions that require further investigation.

### Disclosure

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