LONG-TERM AND CUMULATIVE EFFECTS OF SPORTS CONCUSSION ON MOTOR CORTEX INHIBITION

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OBJECTIVE: Using transcranial magnetic stimulation paradigms, this study investigated motor cortex integrity as a function of an athlete's prior history of concussions.

PATIENTS AND METHODS: Motor cortex excitatory and inhibitory mechanisms were studied in athletes using four different transcranial magnetic stimulation protocols, namely 1) resting motor threshold, 2) intracortical inhibition and intracortical facilitation in a paired-pulse paradigm, 3) excitability of the corticospinal system using an input-output curve, and 4) intracortical inhibition in a cortical silent-period paradigm. Motor-evoked potentials were recorded from the first dorsal interosseous muscle of the right hand.

RESULTS: Cortical silent-period duration in athletes who have experienced multiple concussions was prolonged when compared to that of normal control participants. Linear regression suggested that concussion severity was the main factor explaining motor cortex dysfunction. Moreover, when we retested the athletes, the cortical silent period was more prolonged in those who sustained another concussion after baseline testing had occurred.

CONCLUSION: Findings from this study indicate that sports-related concussions result in long-term motor system dysfunctions that seem to be attributable to subclinical intracortical inhibitory system abnormalities. This study also shows that sustaining subsequent concussions exacerbates this deficit, and thus provides additional support for the contention that the adverse effects of sports-related concussions on intracortical inhibitory systems are cumulative.

KEY WORDS: Cortical silent period, Intracortical inhibition, γ-Aminobutyric acid-B interneuron receptors, Sports concussions, Transcranial magnetic stimulation

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In the United States, an estimated 50,000 to 300,000 contact-sports athletes sustain concussions during the course of a sports season (6). During the last 15 years, the exponentially growing prevalence of sports concussions has greatly promoted research efforts dedicated to the diagnosis, treatment, and recovery process of traumatic brain injuries (TBIs), as they are now considered a major public health concern (19). Although for decades researchers have sought the existence of pervasive impairments in brain function after TBI, very little conclusive evidence has emerged, especially with regard to mild TBI. In fact, most neuropsychological studies (4, 10, 11, 17) suggest that patients recover full cognitive function within 2 to 10 days after a mild head injury.

Despite the seemingly few effects of mild TBI on cognitive function, recent data provide strong evidence that the effects of concussions are cumulative. A recent National Collegiate Athletic Association study showed that contact-sports athletes with a prior history of concussion are three times more likely to sustain subsequent concussion than are athletes with no prior concussion history (16). This study also showed that athletes with a history of more than three concussions recovered more slowly than those who sustained only one concussion. In the same vein, high-school football players who previously sustained a severe concussion that involved loss of consciousness were found to be four times more likely to suffer subsequent Grade 3 (per American Acad-

emy of Neurology guidelines) concussions than players who had never lost consciousness as a result of brain trauma (13). Another study showed that athletes with a history of sports concussion are 9.3 times more at risk of showing signs in three out of the four concussion-severity markers (positive loss of consciousness, anterograde amnesia, retrograde amnesia, and confusion) than others with no history of concussion (9). Taken together, these data show that athletes who experience multiple concussion are more vulnerable to subsequent concussions, and they suffer more severe postconcussion symptoms than athletes with no prior history of concussion.

With regard to the growing literature on the cumulative effects of concussion, recent studies sought to explore the potential long-term impact of concussion on brain function. An epidemiological report (15) recently revealed a fivefold increase in the prevalence of the mild cognitive impairment diagnosis in retired football players. This condition is characterized by early-memory impairment that converts into Alzheimer's disease at a rate of approximately 10 to 20% per year. Other studies conducted with professional and amateur boxers provide additional evidence for the existence of severe long-term sequelae associated with recurrent concussive and subconcussive blows to the head. As a direct consequence of sustaining recurrent concussions throughout their career, it was found that approximately 17% of retired professional boxers developed early symptoms of mild confusion and ataxia that quickly progressed to a "Parkinsonian" cognitive decline (27). In fact, abnormal performance on memory tests, increased motor and speech latencies, dysarthria, pyramidal tract dysfunction, tremor in the head and upper extremities, and behavioral changes are common features associated with what has often been referred to as dementia pugilistica or chronic TBI (27), a brain pathology that has been described solely in boxers. Although recent event-related potential studies have revealed persistent subclinical attention and working-memory abnormalities in asymptomatic concussed athletes (14, 21), no study to date has documented motor system abnormalities in this population. Considering that motor symptoms are typically the earliest clinical manifestation of chronic TBI (27), it seems plausible that the motor system could be affected by repeated concussive blows to the head. To address this issue, transcranial magnetic stimulation (TMS) is a particularly pertinent and useful technique because of its unprecedented sensitivity to central inhibitory and excitatory mechanisms of the motor system (1). Indeed, altered motor system excitability during the acute phase after a minor head injury was recently demonstrated as higher thresholds to single-pulse TMS were reported (8).

The present study was conducted to evaluate whether young, asymptomatic, concussed athletes for whom unremarkable magnetic resonance imaging results were reliably reported across studies (3, 7) would show subclinical motor cortex dysfunction years after their last concussion. In light of the above-mentioned neuropsychological data on the cumulative effects of sports concussions, we hypothesized that athletes with a history of recurrent concussions would show greater subclinical motor system abnormalities than those who sustained only one concussion. Finally, to partially address the issue of cause and effect—namely, that abnormalities in motor cortex function were a premorbid characteristic and may have played a causal role in individuals sustaining sports concussions—that cannot be excluded in retrospective studies of this nature, we sought to prospectively investigate whether sustaining another concussion would result in worsened motor system abnormalities, which would thereby provide additional support for the contention that the effects of concussions are cumulative.

PATIENTS AND METHODS

Study Participants

All 45 participants in this study were active players of the University of Montreal Carabins' football team and were recruited with help from the team physician. The following exclusion criteria were applied to select the athletes who took part in this study: a history of alcohol and/or substance abuse; psychiatric illness; learning disability; significant neurological history (seizure disorder or concussion-related seizures, central nervous system neoplasm, or brain tumor); and TBI unrelated to contact sports. None of the athletes who participated in this study were taking medications at the time of testing. The study was composed of three experimental groups. The first group consisted of 15 asymptomatic athletes who had a history of two or more sports concussions that occurred more than 9 months before testing. The number of concussions sustained ranged from two to five. The second experimental group consisted of 15 athletes who had a history of only one sports concussion, which also had to occur more than 9 months before testing. These two groups were equivalent for the time elapsed since the last concussion (F (1, 28) = 2.38; $P > 0.13$; see *Table 1*). Concussion severity was assessed by the team physician. It varied from Grade 1 (confusion for less than 15 minutes without amnesia or loss of consciousness) to Grade 3 (no loss of consciousness, duration either brief [seconds] or prolonged [minutes]) according to the parameters supplied by the American Academy of Neurology (2). Additionally, all head injuries were classified as minor, with Glasgow Coma Scale scores ranging between 13 and 15. The third control group also consisted of 15 university football players with no history of neurological insult at the time of testing. All three experimental groups were equivalent with regard to age (F (2, 43) = 0.46; $P > 0.63$) and level of education (F (2, 43) = 1.51; $P > 0.23$; see *Table 1*). A standardized concussion-history form was administered to obtain detailed information about the number of previous concussions (if any), approximate date(s) of each concussion, descriptions of the accident(s), nature and duration of relevant postconcussion symptoms (confusion and/or disorientation, retrograde and/or anterograde amnesia, and loss of consciousness), neuroimaging results (if any), and number of days before the individual returned to play (if any). Grades of previous concussions were classified by a sports physician using the practice parameter of the American Academy of Neurology.

PATIENTS AND PROCEDURES

Neuropsychological Assessment

Neuropsychological tests from the National Football League neuropsychological testing program were used to assess multiple aspects of cognitive functioning (25). This battery includes classic neuropsychological tests selected to evaluate attention processes (Pennsylvania State

TABLE 1. Between-group comparisons of demographic and concussion history information[a]

Variables	Groups	Means ± standard deviations	*F* test	*P* value
Age, yr	Control Single Multiple	22.50 ± 2.53 22.94 ± 2.84 23.38 ± 2.63	0.461	>0.63
Education, yr	Control Single Multiple	17.00 ± 1.68 17.75 ± 1.612 17.94 ± 1.73	1.511	>0.23
Time since last concussion, mo	Control Single Multiple	— 59.12 ± 69.52 31.00 ± 22.08	2.379	>0.13
Concussions sustained, no.	Control Single Multiple	— 1 ± 0 2.75 ± 1.29	29.4	<0.001
Concussion severity	Control Single Multiple	— 1.81 ± 0.75 2.13 ± 0.50	1.923	>0.17

[a]Three groups were studied: control athletes with no history of concussion, athletes who had a single concussion, and athletes who had experienced multiple concussions.

University cancellation task), visual scanning and information processing (Color Trails A and B and Symbol Digit Modality Test), visual memory (Brief Test of Visual Memory and incidental memory recall of Symbol Digit Modality Test), verbal memory (Hopkins Verbal Learning Test), visual-motor coordination (Brief Test of Visual Memory), and speech fluency (verbal fluency, phonemic). Neuropsychological testing was completed by a trained neuropsychology student. The test administration and procedures were standardized and uniform for all participants. All scores were within normal ranges and between-group comparisons on neuropsychological test scores revealed no differences among the groups.

Transcranial Magnetic Stimulation Recordings

All participants completed four TMS paradigms that were administered in a single 1-hour session at the University of Montreal Neuropsychology laboratory. Subjects were seated in a comfortable chair. Electromyogram (EMG) recordings were obtained from electrodes placed on the right first dorsal interosseous (index finger) muscle using a belly-tendon montage and were amplified using a Biopac MP150 system (Biopac Systems, Goleta, CA) with a 20-Hz to 1-kHz band-pass filter. The signal was processed on a Macintosh G4 computer (Apple, Cupertino, CA) using AcqKnowledge software (Biopac Systems). A MagPro transcranial magnetic stimulator (Medtronic, Minneapolis, MN) was connected to an 8-cm-diameter, figure-eight coil. The coil was positioned in the optimal position for eliciting contralateral motor-evoked potentials (MEPs) at a 45-degree angle from the midline. For each subject, the optimal coil position for eliciting reproducible MEPs was obtained by slowly moving the coil in 1-cm steps over the preferred area of stimulation of the contralateral motor cortex. This optimal site was marked with washable marker to make sure that the coil was held in the same position throughout the experiment. The following TMS parameters were measured: resting motor threshold, EMG response to paired TMS stimulation, EMG response to single TMS pulses of varying stimulus intensities (input-output curves), and cortical silent-period duration.

Resting Motor Threshold. Several TMS parameters have been developed to assess the overall excitability of the corticospinal system. The resting motor threshold reflects the minimum TMS intensity (usually expressed as a percentage of maximum stimulator output) resulting in MEPs in a fully relaxed target muscle in 5 out of 10 consecutive trials. Recent pharmacological studies suggest that the resting motor threshold reflects neuronal membrane excitability, which is highly dependent on ion-channel conductivity (32). The motor threshold at rest was calculated as the minimal stimulation intensity evoking an MEP of at least 50 μV in 5 out of 10 consecutive trials when TMS was applied to the contralateral M1. In most cases, the resting motor threshold was measured by a reduction from slightly supra-threshold intensities (starting at 60% of the maximum stimulator output) in 1% steps. However, when participants presented with resting motor thresholds higher than 60% of the maximum stimulator output, the resting motor threshold was obtained by increasing stimulation intensity in 3% steps until recorded reproducible MEPs were obtained. The resting motor threshold was then obtained by reducing intensity from these slightly supra-threshold values in 1% steps. A typical MEP elicited by a single pulse is illustrated in *Figure 1A*.

Paired-Pulse TMS Paradigm. Intracortical inhibition (ICI) resulting in suppressed MEPs is obtained in a paired-pulse TMS paradigm when a subthreshold conditioning stimulus over the motor cortex precedes a supra-threshold stimulation by 1 to 6 milliseconds. The maximum suppression is induced by conditioning stimulus intensities ranging from 70% to 90% of the resting motor threshold, whereas higher stimulation intensities engender less inhibition and often less facilitation (1). On the basis of previous animal studies, Kujirai et al. (20) suggested that this suppression in motor activity is mainly the result of the activation of intracortical γ-aminobutyric acid (GABA) interneurons of the primary

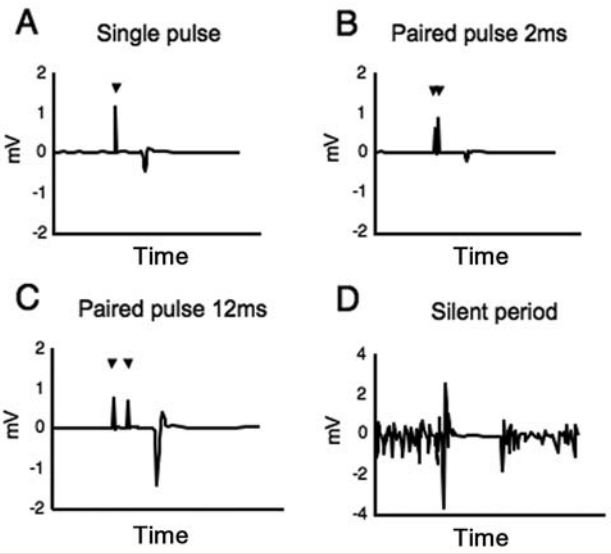

FIGURE 1. A, *a typical MEP as elicited by a single pulse (▼). **B**, a typical MEP resulting from ICI in a paired-pulse paradigm. **C**, a typical MEP resulting from ICF in a paired-pulse paradigm. **D**, a typical CSP as occurred when TMS was delivered over the motor cortex while the subject maintained a voluntary muscle contraction.*

motor cortex. A typical MEP resulting from ICI in a paired-pulse paradigm is illustrated in *Figure 1B*. On the contrary, when the subthreshold conditioning stimulus precedes the supra-threshold stimulus (test stimulus) by 8 to 20 milliseconds, the MEPs elicited by the test stimulus are facilitated when the target muscle is at rest. Although the mechanisms responsible for intracortical facilitation (ICF) are not fully understood, MEP facilitation assessed by the ICF paradigm seems to be mediated by synaptic glutamatergic transmission (22, 32). Possibly, horizontally arranged corticocortical projecting pyramidal cells located in superficial cortical layers mediate ICF (30).

For the purpose of this study, we used short interstimulus intervals (ISIs) of 1, 2, and 3 milliseconds to test ICI, and long ISIs of 6, 9, 12, and 15 milliseconds to study ICF according to the method of Kujirai et al. (20). A subthreshold conditioning stimulus set at 80% of the resting motor threshold preceded a supra-threshold test stimulus. This test stimulus was adjusted to produce an average MEP of 1 mV peak-to-peak amplitude (20). The conditioning stimulus preceded the test stimulus according to seven random ISIs (1, 2, 3, 6, 9, 12, and 15 milliseconds). We also included a test stimulus-alone condition set at approximately 120% of the resting motor threshold to obtain baseline measurements. Ten consecutive trials were performed for each ISI and for the test stimulus-alone condition. The interpulse interval was 6 to 8 seconds. A typical MEP resulting from ICF in a paired-pulse paradigm is illustrated in *Figure 1C*.

Input-Output Curves. Input-output curves are thought to reflect the strength of corticospinal projections, as they are steeper in muscles with larger motor cortex representation (1). Corticospinal excitability was assessed using single TMS pulses of increasing intensities (80%, 90%, 100%, 110%, 115%, 120%, 130%, and 140% of resting motor threshold). Ten consecutive trials were performed for each condition. The order of presentation of the different TMS intensities varied randomly across participants. The interpulse interval was 6 to 8 seconds.

Cortical Silent Period. When TMS is delivered over the motor cortex while the subject maintains a voluntary muscle contraction, a pause in ongoing EMG activities follows the MEP. This pause is called the cortical silent period (CSP) (28). The level of muscle contraction has negligible effects on the duration of the CSP, whereas the intensity of the test stimulus is positively correlated with the CSP duration. Studies on the CSP mechanism tend to suggest that its duration is influenced by several factors. The initial phase of the CSP has often been explained by segmental factors such as the H reflex and the refractory period of the pyramidal tract neurons. However, segmental factors are too short to explain the extended duration of the CSP, which often lasts for more than a few hundred milliseconds. Activation of ICI interneurons mediated by GABA-B receptors located in the motor cortex seems to explain the late phase of the CSP (31). Ten single-pulse stimulations (120% of motor threshold intensity) were applied to the left M1 while the participant maintained a voluntary isometric contraction of the right first dorsal interosseous muscle at approximately 10% of his strength. Maximum right first dorsal interosseous muscle strength, from which we derived the 10% voluntary isometric muscle contraction value, was recorded as participants were asked to push as hard as they could against a digital force gauge in a horizontal right-to-left motion for approximately 15 seconds. The intensity of the muscle contraction was digitized so that participants could regulate their exerted strength to a relatively constant level. The duration of the CSP was calculated using a graphical method as previously described by Garvey et al. (12) and was defined as the period from the onset of EMG suppression until the resumption of sustained post-stimulus EMG activity. A typical CSP is illustrated in *Figure 1D*.

Retesting

Five athletes from the multiple-concussion group sustained a concussion after they were tested for the initial purpose of this study. They all agreed to be retested with the same experimental protocol between 6 and 15 months after their injury to investigate the pervasive effects of sustaining incident concussions on motor system function.

Statistical Analyses

All values are expressed as means plus/minus standard deviations (SDs). EMG data obtained from consecutive recordings were subjected to standard descriptive statistics and were later tested with analysis of variance in all four TMS paradigms. In the paired-pulse paradigm, we computed for each participant a ratio between the mean MEP amplitude elicited by each ISI condition with the mean MEP amplitude elicited by the test stimulus alone. A Greenhouse-Geisser correction for multiple comparisons was applied to both paired-pulse and input-output paradigms. We also computed a series of two-tailed Pearson correlations between CSP duration and concussion history information that was collected for each participant in this study (including time elapsed since the last concussion, concussion severity rated according to American Academy of Neurology standards, and number of concussions sustained). Finally, we computed a linear regression from which we obtained the coefficient of the linear equation (β-coefficient) that provides an estimate of the variables (in this study, the number of concussions sustained or the concussion severity) that best predict the abnormal CSP lengthening in concussed athletes.

RESULTS

Resting Motor Threshold

There was no group difference for motor threshold (F (2, 43) = 0.20; $P > 0.81$). Mean resting motor threshold values were 53% (standard deviation [SD] = 9.53%), 56% (SD = 18.27%), and 53% (SD = 7.19%) for the control, single-concussion athletes, and multiple-concussion athletes groups, respectively (see *Fig. 1A*).

Paired-Pulse Transcranial Magnetic Stimulation

Intracortical Inhibition Condition

Paired-pulse TMS curves for both groups were normal in configuration. In both groups, short ISIs (1, 2, and 3 milliseconds) inhibited the response to the test stimulus. There was no significant interaction between groups (concussed or control participants) and ISI duration for short ISIs eliciting ICI (1, 2, and 3 milliseconds) (F (1, 44) = 1.75; $P > 0.14$) after Greenhouse-Geisser correction. MEP sizes were not found to be significantly different across the three groups for ICI conditions (F (2, 43) = 0.14; $P > 0.86$). As expected, tests of within-subject effects yielded a significant difference in MEP sizes elicited by the three different ISIs of the ICI condition (1, 2, and 3 milliseconds) (F (1, 44) = 5.32; $P < 0.01$).

Intracortical Facilitation Condition

The interaction between groups and the inter-stimulus interval duration for longer ISIs (6, 9, 12, and 15 milliseconds) eliciting ICF were not significant (F (1, 44) = 1.72; $P > 0.12$;

see *Fig. 1D*). MEP sizes for the ICF condition were not statistically different between the three groups (F (2, 43) = 0.42; $P > 0.65$). Tests of within-subject effects revealed a significant difference between ISIs yielding ICF (F (1, 44) = 12.19; $P < 0.01$).

Input-Output Curves

Input-output curves were normal in configuration. In all three groups, EMG responses were larger as TMS intensity increased. The interactions between groups (concussed or control participants) and TMS intensities (90%, 100%, 105%, 110%, 115%, 120%, 130%, and 140% of resting motor threshold) were not found to be significant (F (1, 44) = 1.73; $P > 0.14$) after application of the Greenhouse-Geisser correction for multiple comparisons. Tests of within-subject effects showed that all three groups had significantly larger MEPs as the intensity of the TMS increased (F (1, 44) = 36.39; $P < 0.001$; see *Fig. 1C*).

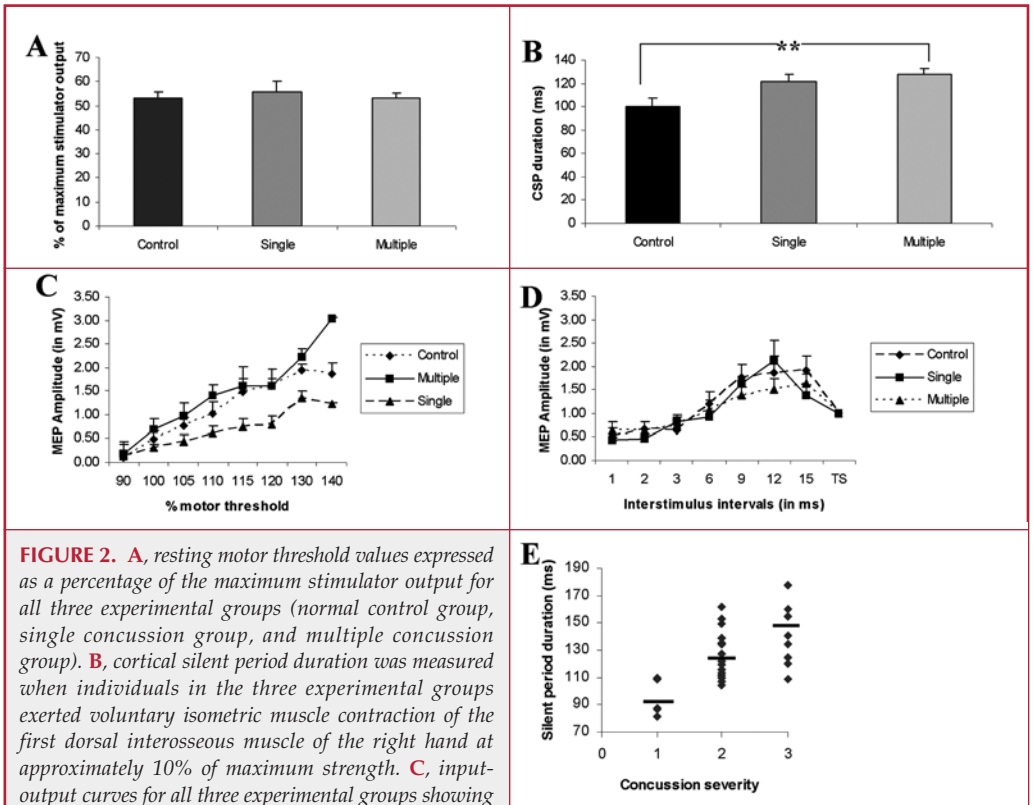

FIGURE 2. **A**, *resting motor threshold values expressed as a percentage of the maximum stimulator output for all three experimental groups (normal control group, single concussion group, and multiple concussion group).* **B**, *cortical silent period duration was measured when individuals in the three experimental groups exerted voluntary isometric muscle contraction of the first dorsal interosseous muscle of the right hand at approximately 10% of maximum strength.* **C**, *input-output curves for all three experimental groups showing the average MEP amplitude as increasing TMS intensities (90%, 100%, 105% 110%, 115%, 120%, 130%, and 140%, expressed as a percentage of the resting motor threshold), were applied to the motor cortex.* **D**, *paired-pulse paradigm showing the average MEP amplitude for all three experimental groups when increasing interstimulus interval durations (1, 2, 3, 6, 9, 12, and 15 ms) separated the conditioning stimulus from the test stimulus.* **E**, *Pearson correlations between CSP duration and concussion severity (Grades 1 to 3) in concussed athletes. Error bars in A–D represent standard error values.*

Cortical Silent-Period Duration

Two raters (both blind to diagnosis) measured CSP durations for all subjects (*Fig. 2*). The length of the CSP was measured from the beginning of the MEP until the onset of ongoing EMG activity. An intra-class correlation coefficient was calculated to determine the inter-rater reliability for CSP durations. A 0.96 correlation coefficient was obtained. A one-way analysis of variance yielded a significant between-group effect (F (2, 43) = 5.12; $P < 0.01$). Tukey honest significant difference post hoc analysis revealed that the CSP duration was significantly prolonged in the group of athletes presenting with recurrent concussions (127.55 ± 26.86 milliseconds) when contrasted with that of the normal control group (100.53 ± 26.09 milliseconds; $P < 0.01$; see *Fig. 1B*), whereas other between-group comparisons did not reach significance.

We computed two-tailed Pearson correlations to investigate whether the length of the silent period appeared to be affected by concussion history information markers such as the time elapsed since the last concussion, the number of concussions sustained, and the severity of the concussions sustained. Among those concussion history markers, it was found that sustaining rather severe concussions was significantly correlated with CSP lengthening (two-tailed Pearson correlation = 0.45; $P < 0.02$; n = 15) in concussed athletes. Other correlations drawn between the TMS-induced CSP and concussion history information were not significant (*Table 2*).

Finally, a linear regression was computed to assess what variable between concussion history and accident severity best predicted the observed abnormal CSP duration in multiple-

TABLE 2. Correlations between concussion history information and duration of the cortical silent period in concussed athletes[a]

Concussion history marker	Condition	Correlations	*P* value
History	Number of concussions	0.133	>0.48
Severity	Concussion grade[a]	0.448	<0.02
Date	Date of last concussion	–0.169	>0.37

[a] Concussion severity was measured by grade, in accordance with the American Academy of Neurology practice parameters (2).

TABLE 3. Length of cortical silent period at Times 1 and 2 compared with concussion history information

Subject no.	No. of concussions	Time elapsed, mo	Severity, grade[a]	Time 1	Time 2
1	3	7	3	120.80 ± 11.27	132.30 ± 12.76
2	5	6	2	207.65 ± 14.85	214.75 ± 16.04
3	3	7	3	90.15 ± 10.80	118.62 ± 8.43
4	4	7	1	154.20 ± 11.27	158.51 ± 10.77
5	3	15	2	144.26 ± 10.73	155.30 ± 9.52

[a] Concussion severity was measured by grade in accordance with the American Academy of Neurology practice parameters (2).

concussion athletes. This analysis revealed that the severity of concussions sustained, as rated according to the American Academy of Neurology practice parameter, was a better predictor of abnormal CSP lengthening observed in multiple-concussion athletes than the number of concussions per se (β-coefficient for concussion groups = 0.08; $P > 0.637$; β-coefficient for concussion severity = 0.435; $P < 0.019$; see *Fig. 1E*).

Retesting

Although repeated-measures analysis of variance revealed equivalent resting motor threshold (F (1, 4) = 0.38; $P > 0.57$), paired-pulse ICI (F (1, 4) = 1.31; $P > 0.32$), ICF (F (1, 4) = 1.61; $P > 0.25$), input-output curves (F (1, 4) = 2.82; $P > 0.11$), and neuropsychological test scores at Testing Date 1 (Time 1) to be comparable with those obtained at Testing Date 2 (Time 2), the length of the CSP was found to be significantly prolonged as a result of the incident concussion (F (1, 4) = 8.80; $P < 0.05$; *Table 3*).

DISCUSSION

Results from this study suggest for the first time that sports concussions result in chronic subclinical motor system dysfunctions that are linked to intracortical inhibitory system abnormalities. Three main sources of evidence are provided in this study to support this finding: 1) the duration of the CSP was significantly prolonged in those athletes with a history of concussions; 2) sustaining subsequent concussions exacerbates CSP abnormalities; and 3) CSP duration is positively correlated with the severity of concussions sustained.

The primary objective of this study was to investigate the excitability of the primary motor cortex as a function of an athlete's concussion history. Using TMS, we identified a prolonged CSP duration in asymptomatic athletes who presented with a history of recurrent concussions. However, when computing linear regressions to determine the variable that best predicts the observed CSP lengthening in multiple-concussion athletes, we found that most of this abnormality could be attributed to concussion severity rather than belonging to the single or multiple concussion groups. These linear regressions were performed because our data showed that athletes with a history of multiple concussions tended to have sustained more severe concussions than athletes in the single-concussion group.

When we prospectively examined the effects of recurrent concussions in a small group of multiple-concussion athletes who were retested using the same experimental protocol, we found that the CSP was significantly prolonged after an athlete sustained another concussion, which suggests that intracortical inhibitory interneuron receptors of the motor system may be particularly vulnerable to the effects of sports concussions.

Another major finding was that the observed CSP duration lengthening in multiple-concussion athletes seemed to remain unaffected by the time elapsed since the last accident, as evidenced by the near-zero Pearson correlation value that was obtained between these two variables. This strongly suggests that the underlying intracortical inhibitory mechanism that is presently thought to modulate the duration of the CSP remains significantly altered in asymptomatic young athletes regardless of the time elapsed since the last concussion. Taken together, these results suggest that sustaining concussions of a more severe nature generates significant abnormalities in motor cortex functioning that persist far beyond the acute phase of the injury.

One possible neurophysiological substrate of CSP duration increase in concussed athletes may lie in an impaired GABA-B receptor system. The latter part of the CSP has been attributed to activity of intracortical inhibitory systems of the primary motor cortex, whereas spinal inhibition contributes to its early part (18). Evidence that the late part of the CSP is caused by long-lasting cortical inhibition mediated by GABA-B receptors comes from pharmacological studies. Tiagabine, a GABA reuptake inhibitor, lengthens the CSP (29). Furthermore, L-DOPA and dopamine agonists also appear to lengthen CSP duration (26), thereby strengthening the claim that GABA (particularly GABA-B) receptors are crucial for the determination of CSP duration. On the basis of these findings, it appears that concussions alter the efficacy of GABA-B receptor systems, perhaps contributing to rendering the brain more vulnerable to subsequent traumatic events. However, a recent pharmacological study (23) showed no specific effect of having ingested a selective GABA-B receptor agonist on the modulation of the CSP. In light of emerging findings that suggest CSP abnormalities constitute a particularly sensitive measure of motor system dysfunctions that are observed in various brain pathologies, this emphasizes the need to gain a better grasp of the underlying mechanisms of the CSP.

In a previous study conducted by Chistyakov et al. (8), CSP was also found to be significantly prolonged in patients with mild to moderate head injury when compared with matched controls 2 weeks after the accident. However, results from that study suggest that CSP duration was not altered in concussed patients who sustained minor head injuries, this severity grading being equivalent to that of concussed athletes recruited for the present study. This discrepancy could be explained by a variety of factors such as different methodologies (different TMS intensities were used to measure CSP duration; also, we used a circular coil), differing patient populations (concussed university football players versus head-injury patients recruited as they were seeking medical attention), and different times of testing (9 months after the injury versus within 2 weeks of the injury). On the other hand, the intriguing possibility is raised that CSP prolongation could be triggered later after head trauma. Contrary to the findings of Chistyakov et al. (8), our results did not reveal differences in corticospinal system excitability based on resting motor threshold measurements between concussed and control athletes. One explanation could be that the concussed athletes recruited for our study had sustained their injuries more than 9 months before testing, whereas the minor-to-moderate head-injury patients from Chistyakov et al.'s study were tested 2 weeks after their injuries. When results from the work of Chistyakov et al. (8) and the present study are taken together, one might speculate that the motor threshold paradigm is especially sensitive to the metabolic imbalances that are known to occur as part of the acute effects of concussions (24), whereas this motor system abnormality may return to normal functioning after having benefited from spontaneous recovery.

Interestingly, recent neuropsychological and event-related potentials studies found that athletes with asymptomatic concussion showed altered cognitive function despite normal results on classic neuropsychological tests that are used as the gold standard in the assessment of cognitive function after sports concussion (5, 14). Similarly, the altered CSP duration found in this study in asymptomatic concussed athletes who presented with normal scores on neuropsychological tests adds additional support for the contention that sports concussions result in persistent brain function alterations that cannot be detected by standard neuropsychological tests. Studies that examine athletes' ability to perform more refined motor tasks are needed to determine the clinical significance of these TMS findings.

An important limitation of the present study is the lack of imaging results. In fact, one possible explanation for the present findings could be that the CSP prolongation is the result of structural damage rather than sports concussion. However, knowing that only 10% of all minor/mild head injury patients show magnetic resonance imaging abnormalities related to trauma (3, 8), it is highly improbable that structural damage alone could explain the observed CSP prolongation in all five patients who sustained a subsequent concussion within the study period. Nonetheless, the addition of structural imaging would be instrumental in future studies to systematically address this issue.

Findings from this study show that sports concussions result in long-term motor system dysfunctions that seem to be attributable to subclinical intracortical inhibitory system abnormalities. This study also shows that sustaining subsequent concussions exacerbates this deficit, thus providing support for the contention that the adverse effects of sports concussions on intracortical inhibitory systems are cumulative.

REFERENCES

1. Abbruzzese G, Trompetto C: Clinical and research methods for evaluating cortical excitability. **J Clin Neurophysiol** 19:307–321, 2002.
2. Anonymous: Practice parameter: The management of concussion in sports (summary statement). Report of the Quality Standards Subcommittee. **Neurology** 48:581–585, 1997.
3. Aubry M, Cantu R, Dvorak J, Graf-Baumann T, Johnston KM, Kelly J, Lovell M, McCrory P, Meeuwisse WH, Schamasch P, Concussion in Sport (CIS) Group: Summary and agreement statement of the 1st International Symposium on Concussion in Sport, Vienna 2001. **Clin J Sport Med** 12: 6–11, 2002.
4. Barth JT, Alves WA, Ryans TV, Macchiocchi SN, Rimel RE, Jane JA, Nelson WE: Mild head injury in sports: Neuropsychological sequelae and recovery of function, in Levin HS, Eisenberg HM, Benton AL (eds): *Mild Head Injury*. New York, Oxford University Press, 1989, pp 257–275.
5. Bernstein DM: Information processing difficulty long after self-reported concussion. **J Int Neuropsychol Soc** 8:673–682, 2002.
6. Centers for Disease Control and Prevention: Sports-related recurrent brain injuries—United States. **JAMA** 277:1190–1191, 1997.
7. Chen JK, Johnston KM, Frey S, Petrides M, Worsley K, Ptito A: Functional abnormalities in symptomatic concussed athletes: An fMRI study. **Neuroimage** 22:68–82, 2004.
8. Chistyakov AV, Soustiel JF, Hafner H, Trubnik M, Levy G, Feinsod M: Excitatory and inhibitory corticospinal responses to transcranial magnetic stimulation in patients with minor to moderate head injury. **J Neurol Neurosurg Psychiatry** 70:580–587, 2001.
9. Collins MW, Lovell MR, Iverson GL, Cantu RC, Maroon JC, Field M: Cumulative effects of concussion in high school athletes. **Neurosurgery** 51:1175–1181, 2002.
10. Dikmen S, Mclean A, Temkin N: Neuropsychological and psychosocial consequences of minor head injury. **J Neurol Neurosurg Psychiatry** 49:1227–1232, 1986.
11. Echemendia RJ, Putukian M, Mackin RS, Julian L, Shoss N: Neuropsychological test performance prior to and following sports-related mild traumatic brain injury. **Clin J Sport Med** 11:23–31, 2001.
12. Garvey MA, Ziemann U, Becker DA, Barker CA, Bartko JJ: New graphical method to measure silent periods evoked by transcranial magnetic stimulation. **Clin Neurophysiol** 112:1451–1460, 2001.
13. Gerberich SG, Priest JD, Boen JR, Straub CP, Maxwell RE: Concussion incidences and severity in secondary school varsity football players. **Am J Public Health** 73:1370–1375, 1983.
14. Gosselin N, Theriault M, Leclerc S, Montplaisir J, Lassonde M: Neurophysiological anomalies in symptomatic and asymptomatic concussed athletes. **Neurosurgery** 58:1151–1161, 2006.
15. Guskiewicz KM, Marshall SW, Bailes J, McCrea M, Cantu RC, Randolph C, Jordan BD: Association between recurrent concussion and late-life cognitive impairment in retired professional football players. **Neurosurgery** 57:719–726, 2005.
16. Guskiewicz KM, McCrea M, Marshall SW, Cantu RC, Randolph C, Barr W, Onate, Kelly JP: Cumulative effects associated with recurrent concussion in collegiate football players: The NCAA concussion study. **JAMA** 290:2549–2555, 2003.
17. Hinton-Bayre AD, Geffen G: Severity of sports-related concussion and neuropsychological test performance. **Neurology** 59:1068–1070, 2002.
18. Inghilleri M, Berardelli A, Cruccu G, Manfredi M: Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. **J Physiol** 466:521–534, 1993.

19. Kelly JP: Traumatic brain injury and concussion in sports. **JAMA** 282:989–991, 1999.
20. Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD: Corticocortical inhibition in human motor cortex. **J Physiol** 471:501–519, 1993.
21. Lavoie ME, Dupuis F, Johnston KM, Leclerc S, Lassonde M: Visual p300 effects beyond symptoms in concussed college athletes. **J Clin Exp Neuropsychol** 26:55–73, 2004.
22. Liepert J, Schwenkreis P, Tegenthoff M, Malin JP: The glutamate antagonist riluzole suppresses intracortical facilitation. **J Neural Transm** 104:1207–1214, 1997.
23. McDonnell MN, Orekhov Y, Ziemann U: The role of GABA(B) receptors in intracortical inhibition in the human motor cortex. **Exp Brain Res** 173:86–93, 2006.
24. Mendez CV, Hurley RA, Lassonde M, Zhang L, Taber KH: Mild traumatic brain injury: Neuroimaging of sports-related concussion. **J Neuropsychiatry Clin Neurosci** 17:297–303, 2005.
25. Pellman EJ, Lovell MR, Viano DC, Casson IR, Tucker AM: Concussion in professional football: Neuropsychological testing—part 6. **Neurosurgery** 55:1290–1305, 2004.
26. Priori A, Berardelli A, Inghilleri M, Accornero N, Manfredi M: Motor cortical inhibition and the dopaminergic system. Pharmacological changes in the silent period after transcranial brain stimulation in normal subjects, patients with Parkinson's disease and drug-induced parkinsonism. **Brain** 117:317–323, 1994.
27. Rabadi MH, Jordan BD: The cumulative effect of repetitive concussion in sports. **Clin J Sport Med** 11:194–198, 2001.
28. Terao Y, Ugawa Y: Basic mechanisms of TMS. **J Clin Neurophysiol** 19:322–343, 2002.
29. Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J: Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. **J Physiol** 517:591–597, 1999.
30. Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W: Effects of antiepileptic drugs on motor cortex excitability in humans: A transcranial magnetic stimulation study. **Ann Neurol** 40:367–378, 1996.
31. Ziemann U, Netz J, Szelenyi A, Homberg V: Spinal and supraspinal mechanisms contribute to the silent period in the contracting soleus muscle after transcranial magnetic stimulation of human motor cortex. **Neurosci Lett** 156:167–171, 1993.
32. Ziemann U, Tergau F, Wischer S, Hildebrandt J, Paulus W: Pharmacological control of facilitatory I-wave interaction in the human motor cortex. A paired transcranial magnetic stimulation study. **Electroencephalogr Clin Neurophysiol** 109:321–330, 1998.

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COMMENTS

Transcranial magnetic stimulation (TMS) has become increasingly useful for diagnostic, therapeutic, and research approaches to noninvasively investigate the corticospinal tract (8). As a diagnostic tool for neurological disorders, it can be used to characterize lesions that affect the corticospinal tract (2). TMS primarily plays a role as an adjunct to imaging studies. Interestingly, in this study, the authors are able to use TMS to provide information that may be otherwise unattainable, as both concussed athletes and patients with mild traumatic brain injury (mTBI) may not have any objective abnormalities on magnetic resonance imaging scans or deficit after exhaustive neuropsychological testing.

In this study, TMS is used to assess college athletes with zero, single, or multiple concussions. The authors present a well-designed study with a relatively large number of concussed patients and were able to follow patients who received another concussion during the testing period. Neuropsychological testing showed no difference between groups. However, differences were found using the TMS cortical silent period (CSP), which is the electrical silence which occurs after a stimulus is given. It lasts approximately 200 to 300 ms and is dependent on stimulus intensity (2). Athletes with multiple and/or severe concussions were noted to have significantly prolonged CSPs. Furthermore, the duration of the CSP lengthened significantly in patients who experienced another concussion during the test period. The mechanisms leading to CSP duration prolongation are not completely understood and seem to be affected both by cortical and subcortical lesions (1–3).

The exciting finding in this study is that CSP may provide a more sensitive means of evaluating the severity of mTBI. The further prolongation of CSP duration with repetitive concussions is intriguing. This is not the first time TMS has been used to demonstrate cortical changes after mTBI (9). CSP duration was also high between subject variability and can be affected by age, drugs, and stimulation parameters (1–5). It follows that a much larger number of patients would need to be studied and the follow-up period extended to determine the clinical relevance of these findings. That being said, these electrophysiological abnormalities may correlate with the subjective description of mTBI patients as "not quite right" or "different than before" by people close to them, despite no objective findings on imaging or neuropsychological testing. In athletes, mTBI patients, and other neurosurgical patients, these subjective changes are often underappreciated by clinicians and others who assess patients' functional disability, perhaps because there is presently little treatment to offer. These studies could lead to better return-to-play recommendations and post-concussive management.

A better understanding of these electrophysiological abnormalities may lead to treatments geared at normalizing these data as an objective measure of improvement. CSP duration, for example, is noted to be altered by drugs affecting the γ-aminobutyric acid and dopaminergic systems (7). The effect, if any, of rehabilitative therapies has not been established. TMS has provided us with an abundance of electrophysiological data and may even be a means to treat concussion (6). The question becomes how to effectively use it to augment diagnostic and treatment options.

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1. Chistyakov AV, Soustiel JF, Hafner H, Trubnik M, Levy G, Feinsod M: Excitatory and inhibitory corticospinal responses to transcranial magnetic stimulation in patients with minor to moderate head injury. **J Neurol Neurosurg Psychiatry** 70:580–587, 2001.
2. Curra A, Modugno N, Inghilleri M, Manfredi M, Hallett M, Berardelli A: Transcranial magnetic stimulation techniques in clinical investigation. **Neurology** 59:1851–1859, 2002.
3. Liepert J, Restemeyer C, Kucinski T, Zittel S, Weiller C: Motor strokes: The lesion location determines motor excitability changes. **Stroke** 36:2648–2653, 2005.
4. Oliviero A, Profice P, Tonali PA, Pilato F, Saturno E, Dileone M, Ranieri F, Di Lazzaro V: Effects of aging on motor cortex excitability. **Neurosci Res** 55:74–77, 2006.
5. Orth M, Rothwell JC: The cortical silent period: intrinsic variability and relation to the waveform of the transcranial magnetic stimulation pulse. **Clin Neurophysiol** 115:1076–1082, 2004.
6. Pape TL, Rosenow J, Lewis G: Transcranial magnetic stimulation: A possible treatment for TBI. **J Head Trauma Rehabil** 21:437–451, 2006.
7. Priori A, Berardelli A, Inghilleri M, Accornero N, Manfredi M: Motor cortical inhibition and the dopaminergic system. Pharmacological changes in the silent

period after transcranial brain stimulation in normal subjects, patients with Parkinson's disease and drug-induced parkinsonism. **Brain** 117:317–323, 1994.
8. Rossini PM, Rossi S: Transcranial magnetic stimulation: Diagnostic, therapeutic and research potential. **Neurology** 68:484-488, 2007.
9. Takeuchi N, Ikoma K, Chuma T, Matsuo Y: Measurement of transcallosal inhibition in traumatic brain injury transcranial magnetic stimulation. **Brain Inj** 20:991–996, 2006.

De Beaumont et al. have presented their results of using TMS to investigate motor cortex integrity in three groups of asymptomatic, Canadian university football players: those with no history of concussion, those with a history of one concussion, and those with two or more previous concussions. Based on their study, de Beaumont et al. noted prolonged CSPs in athletes with a previous history of concussions, exacerbation of CSP abnormalities after repeated concussions, and the positive correlation of CSP abnormalities with concussion severity.

The authors are to be commended for their novel approach to examining the intermediate and cumulative effects of mTBI in an at risk population. With more than 1.5 million participants in middle school and high school football programs in the United States and 75,000 participants in the collegiate ranks (1), a significant proportion of these individuals will sustain some type of brain injury during the course of a season.

Although all of the participants in this study were asymptomatic by neuropsychological testing, the results from this study are eye-opening and may provide one more part of a much larger and more complicated picture. Multiple incidences of mTBI may predispose individuals to accelerated neurodegenerative disorders. Given the increased attention that this subject has recently received in the lay press, it is important for brain injury specialists to continue to explore any and all possible ramifications of sustaining repeated mTBI. With more knowledge, athletic associations will be able to institute policies at each competitive level directed at minimizing the chances for debilitating, long-term neurological sequelae that may compromise the future quality of life of their charges.

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1. Mueller FO: Catastrophic head injuries in high school and collegiate sports. **J Athl Train** 36:312–315, 2001.

The authors have used conditioning test TMS of the primary motor cortex to detect changes in the excitability of the motor cortex in athletes who had sustained concussions. Larger changes were detected in individuals who had sustained multiple concussions. This work adds to a growing body of evidence that a cerebral concussion produces physiological and probably physical changes in the brain.

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