Cortical Excitability in Obstructive Sleep Apnea Syndrome: Transcranial Magnetic Stimulation Study

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Study Objective: To investigate cortical motor area function in patients with obstructive sleep apnea syndrome (OSAS) during the daytime.

Design: The day after a nocturnal polysomnography, transcranial magnetic stimulation (TMS) of the motor cortex was performed recording Motor Evoked Potential from the first dorsal interosseous muscle of the dominant hand. We evaluated: 1) the relaxed motor threshold (RMT), 2) the threshold of the cortical silent period (CSP), 3) the duration of CSP elicited by five stimulus intensities (95%, 100%, 105%, 130%, and 150% of RMT). To estimate the influence of waking on TMS, recordings were performed five times in a day. The Epworth Sleepiness Scale (ESS), and Stanford Sleepiness Scale (SSS) were also measured.

Setting: The study was carried out in the Sleep and Evoked Potentials laboratories of the Don C. Gnocchi Foundation (ONLUS IRCCS) Pozzolatico, Florence, Italy.

Patients: 10 patients with OSAS and 10 healthy volunteers.

Intervention: N/A

Measurements and Results: In OSAS patients, ESS and SSS were significantly higher than in controls. Patients had a longer duration of CSP at 95%, 100%, and 105% RMT intensity at almost recording hours; with 130% of RMT stimuli intensity OSAS patients were significantly different from 10% from controls and with 150% of RMT intensity the difference did not reach significativity. PaCO2 was significantly correlated with CSP duration elicited at 10% with 95%, 100% and 105% of RMT stimulus intensities.

Conclusions: We found alterations of motor cortical excitability in OSAS patients during the daytime. We believe that PaCO2 levels, acting probably on various ion channels or metabolic pathways, may change the excitability of motor cortex modifying excitatory and inhibitory cortical circuits.

Keywords: Obstructive sleep apnoea, Transcranial magnetic stimulation, cortical silent period, hypoxia, hypercapnia

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INTRODUCTION

OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS) IS CHARACTERISED BY RECURRENT PARTIAL OR COMPLETE OBSTRUCTION OF THE UPPER AIRWAY resulting in decreased arterial oxygen saturation and transient arousals with marked disruption of sleep. Daytime sleepiness, fatigue, and neuropsychologic impairment are common clinical features.1,2

Sleep-related recurrent hypoxic episodes may account for the OSAS-associated alterations of both the peripheral1 and autonomic4 nervous systems. It has also been shown that nocturnal hypoxemia2 and hypercapnia2 may produce cognitive deficits in OSAS patients.

Neurophysiological methods provide a valuable tool for detecting clinical and subclinical alterations of the nervous system. Alterations of event-related potentials paralleling impairment of cognitive functions have been reported in patients with OSAS,6,7 suggesting alterations of cortical associative areas. It is likely that alterations of motor cortical excitability may also occur.

Transcranial magnetic stimulation (TMS) is now an established method to noninvasively monitor corticospinal function.8 TMS uses brief strong magnetic fields to induce an electric current in the motor cortex, producing a motor evoked potential (MEP), followed by a period of inhibition in muscle activity termed cortical silent period (CSP).9 The TMS can be used to study in vivo the physiology of the human brain to assess excitatory and inhibitory intracortical circuits.8 The threshold for producing MEP reflects the excitability of the central core of neurones, while CSP reflects the activity of GABAergic inhibitory circuits.8,10-11 Thus, changes in cortical excitability may represent an early and quantifiable marker of dysfunction of the motor cortex.

Horne12 has hypothesized that dysfunction of the motor system can cause sleep-related motor suppression of pharyngeal muscle activity, leading to apneic-hypopneic events. To explore the cortico-motoneuron physiology in this syndrome, we assessed motor cortical excitability using TMS. We reasoned that if Horner’s hypothesis is valid, an increase in resting motor threshold, or changes in the duration of the CSP, or both, could be present in patients with OSAS. Because cortical excitability may be influenced by the level of vigilance,13 we studied both healthy subjects and patients with OSAS 5 times during the day, in order to control for this confounding factor.

Patients and Methods

We studied 10 OSAS patients (9 men, ranging in age from 31 to 67 years; mean age: 56 years) with no clinical evidence of cardiac or pulmonary disease. They had no chronic obstructive pulmonary disease. Patients with history of head injury, cerebral ischemia, encephalitis, or alcohol or drug abuse were excluded. Patients were not taking central nervous system active drugs nor had they previously had positive airway pressure treatment. Ten healthy volunteers (8 men, ranging in age from 31 to 61 years,
mean age: 47 years) were studied as a control group. The study was approved by the local ethics committee, and subjects gave their informed consent prior to participation in the study.

Sleep Studies

The night before TMS, all subjects underwent 1 night of polysomnography. Standard parameters were monitored during the sleep studies, including electroencephalograms (F4-A1, C4-A1, O2-A1) right and left electrooculography, chin electromyography, snoring into a microphone, chest and abdominal wall motion by means of respiratory inductive plethysmography, airflow by means of oronasal thermistors, oxyhemoglobin saturation (SaO2) by pulse oximetry, and electrocardiogram. Recordings were made with the System 4100 SOMNOSTAR (SensorMedics Corporation-Bilthoven-The Netherlands). Polysomnographic data were reviewed manually; sleep scoring was obtained by visual analysis, according to Rechtschaffen and Kales14 criteria, and the following parameters were evaluated: stage 1 and 2 non-rapid eye movement (NREM) sleep as a percentage of total sleep time; stage 3 and 4 NREM as a percentage of total sleep time; and stage rapid eye movement (REM) sleep as percentage of total sleep time. A movement arousal, scored by visual analysis only, was defined as the abrupt appearance of an alpha rhythm in the electroencephalogram during a sleep epoch, accompanied by an increase in electroencephalogram activity lasting for at least 2 seconds. Cessation of airflow for 10 seconds was defined as apnea. Hypopnea was defined as a 50% reduction in airflow for 10 seconds associated with a 4% fall in SaO2 and/or an arousal. The following respiratory parameters were evaluated: respiratory disturbance index, defined as the average number of apneas and hypopneas per hour of sleep; mean nocturnal O2 saturation (mean SaO2), percentage of recording time spent with SaO2 <90% (t90), and minimal nocturnal O2 saturation (min SaO2) during sleep. The criteria for the diagnosis of OSAS was a respiratory disturbance index ≥ 10.

The global degree of daytime sleepiness was measured with the Epworth Sleepiness Scale.15 To exclude other sleep disorders, the Pittsburgh Sleep Quality Index was determined.16

The following measurements were performed during wakefulness. Arterial blood samples were taken only once in the morning while the subjects were breathing room air; oxygen (PaO2) and carbon dioxide (PaCO2) tensions were determined (IL Instrumentation 1301). Routine spirometry, using a water-sealed spirometer (Pulmonet III; Sensormedics Corp., Yorba Linda, CA), was obtained with subjects wearing a nose clip in a seated position.

Transcranial Magnetic Stimulation Studies

The subjects were studied while sitting in an armchair in a quiet room. The TMS studies were conducted according to the standard criteria published by the International Federation of Clinical Neurophysiology.17 We used monophasic electromagnetic stimulators (Magstim 200; Magstim Co., Whitland, Dyfed, UK) with a round flat coil centered horizontally at the vertex. The MEPs were recorded from first dorsal interosseous muscle of the dominant hand with surface electrodes (BIONEN, Firenze, Italy). A Medelec Synergy (version 8.2) machine (Oxford Instruments Medical Systems, Old Woking, UK) amplified (0.1-5 mV) and filtered (10Hz-3kHz) the signal, then stored it on hard disk. The following variables were determined: (1) absolute latency of MEP, (2) central motor transmission time obtained as the difference between the absolute latency of the MEP elicited by TMS on the skull and the latency of MEP elicited by TMS on the cervical spinal cord; (3) the size of the MEPs induced by TMS, measured as a percentage of the compound motor action potential elicited by peripheral stimulation of the ulnar nerve (compound motor action potential/MEP); (4) relaxed motor threshold (RMT), defined as the minimum stimulator intensity that evoked at least 50% of responses with an amplitude > 100 µV (sensitivity 0.1 mV/division, analysis time 100 milliseconds) after 10 consecutive stimuli in the relaxed first dorsal interosseous muscle; (5) duration of CSP (sensitivity 1 mV/D, analysis time 1 s with 200 ms of preanalysis). Because of the relationship between stimulus intensity and CSP length of duration, we used magnetic shocks of different intensities of stimulator with respect to RMT value (95%RMT, 100%RMT, 105%RMT, 130%RMT, and 150%RMT). A sphygmomanometer was used for monitoring the appropriate level of muscle preactivation. The subjects squeezed the partially inflated cuff between their extended first and second finger at strength of 30% of maximum voluntary contraction and were instructed to sustain their contraction even after having perceived magnetic shock. The amount of contraction was expressed in mmHg. The duration of CSP ranged from stimulus artifact to reappearance of continuous electromyogram activity with an amplitude of at least 50% of electromyogram activity of the preactivated first dorsal interosseous muscle; (6) threshold of the CSP defined as the minimum stimulator intensity that evoked 3 CSPs with a duration ≥ 19 milliseconds (sensitivity 1 mV/D, analysis time 1 second with 200 milliseconds of preanalysis) after 5 consecutive stimuli.

To estimate the influence of wakening, TMS recording was performed every 2 hours during the daytime (10:00 AM; 12:00 AM; 2:00 PM; 4:00 PM; 6:00 PM). Before each recording, the level of sleepiness was tested by Stanford Sleepiness Scale.18 All subjects were asked to refrain from drinking beverages containing caffeine or alcohol and from sleeping during the test day. Study design is schematically represented in Figure 1.

Statistical Analysis

Sleep and TMS parameters were used as dependent variables. Results were analyzed for each recording session and stimulus intensity by repeated measurements (ANOVA). The intersubject factor was Group (2 levels: Control, OSAS). Intrasubject factors were hour of recording (Time, 5 levels: 10 AM, 12 AM, 2 PM, 4 PM, 6 PM) for Stanford Sleepiness Scale, RMT, threshold of the CSP, and the stimulus intensity for CSP (Intensity, 5 levels: 95% RMT, 100% RMT, 105% RMT, 130% RMT, and 150% RMT). The univariate solution was obtained after correction for Greenhouse-Geisser factor, whenever appropriate, to protect against Type I errors associated with nonsphericity of data. In each case, the approximate F value associated with the univariate test is reported. Variables that showed significant main effects or significant interactions (P < .05) were subjected to posthoc testing (Scheffé) using an α level of less than .05.

We used Pearson correlation coefficient for regression analysis between TMS values and the following parameters: sleep stages, arousal index, respiratory disturbance index, measures of nocturnal (mean SaO2, min SaO2, t90), daytime PaO2, and PaCO2, and sleepiness data (Epworth Sleepiness Scale, Stanford Sleepiness Scale). The StatView Statistical Package (SAS Institute, Inc., Cary, NC) was used.

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RESULTS

Subjects characteristics, results of nocturnal polysomnography, arterial blood-gas values, and respiratory functional data are summarized in Table 1. Respiratory functional data were similar in patients and controls.

Patients exhibited a marked disruption of sleep with an increase in percentage of sleep stages 1 and 2 and a decrease of sleep stages 3, 4, and REM. OSAS showed an increased number of apnea-hypopnea events and phasic nocturnal oxygen desaturation; mean \( \text{SaO}_2 \) and min \( \text{SaO}_2 \) values were lower, and t90 higher in patients. In the morning, \( \text{PaCO}_2 \) was significantly higher (\( P < .05 \)) and \( \text{PaO}_2 \) lower (\( P < .0001 \)) in patients compared with controls.

The average Epworth Sleepiness Scale score was significantly higher (\( P < .01 \)) in OSAS patients (mean value 10; range 2-21) than in controls (mean value 5.5; range 2-11). At all recording hours, the Stanford Sleepiness Scale average score was significantly higher in patients than controls (3.3 ±1.4 versus 1.5 ±0.6 controls [Group: \( F_{1,25} = 10.05, P = .003 \)]. No significant differences in standard TMS data (absolute latency of MEP, central motor transmission time, compound motor action potential/ MEP) or in RMT values were found (Table 2) between patients and controls. In turn, CSP showed a longer duration in patients than controls (Group: \( F_{1,18} = 11.6, P = .003 \)) (Figure 2; Table 3).

The CSP duration in patients and controls was significantly related to stimulus intensity (Group × Intensity: \( F_{4,25} = 2.94, P = .02 \)). Actually, a posthoc analysis showed that the CSP duration was significantly longer in patients than controls with stimulus of 95% RMT, 100% RMT, and 105% RMT intensity at almost all recording times (Figure 3). Using stimulus intensities of 130% and 150% of RMT, the patients showed a CSP of longer duration, especially in the morning, but differences compared with the

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**Table 1**—Descriptive, Polysomnographic, Respiratory Function Data, and Morning Data of Controls and Patients with Obstructive Sleep Apnea Syndrome

<table>
<thead>
<tr>
<th>Data</th>
<th>Value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSAS</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>Subjects, no.</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Mean age, y (range)</td>
<td>56.0 (31-67)</td>
<td>47.0 (31-61)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.4-57.8</td>
<td>19.0-30.0</td>
</tr>
<tr>
<td>Respiratory function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, %</td>
<td>94.2±14.6</td>
<td>110.6±20.3</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>76.2±5.13</td>
<td>77.3±4.1</td>
</tr>
<tr>
<td>FVC, l</td>
<td>96.9±17.84</td>
<td>121.0±21.3</td>
</tr>
<tr>
<td>SaO₂, % (range)</td>
<td>94.0±2.1(91-97)</td>
<td>97.5±2.1(96-99)</td>
</tr>
<tr>
<td>Mean nocturnal</td>
<td>76.3±6.8(61-84)</td>
<td>92±1.4(88-96)</td>
</tr>
<tr>
<td>Mean minimum</td>
<td>17.3±13.0(1-40)</td>
<td>1.5±0.7(1-2)</td>
</tr>
<tr>
<td>Polysomnography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>360.7±27.9</td>
<td>367.0±31.1</td>
</tr>
<tr>
<td>Sleep efficiency,%</td>
<td>90.8±6.3</td>
<td>92.4±2.5</td>
</tr>
<tr>
<td>Mean RDI, no./h</td>
<td>47.3±19.7</td>
<td>2.5±1.0</td>
</tr>
<tr>
<td>Microarousal, no./h</td>
<td>46.6</td>
<td>2.6±0.8</td>
</tr>
<tr>
<td>Sleep stage, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wake</td>
<td>6.3</td>
<td>3.8</td>
</tr>
<tr>
<td>1-2</td>
<td>79.4</td>
<td>52.5</td>
</tr>
<tr>
<td>3-4</td>
<td>9.8</td>
<td>30.4</td>
</tr>
<tr>
<td>REM</td>
<td>2.9</td>
<td>13.0</td>
</tr>
<tr>
<td>Morning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{PaO}_2 ), mmHg (range)</td>
<td>75.5 (61.0-90.4)</td>
<td>90.7 (82.7-96.5)</td>
</tr>
<tr>
<td>( \text{PaCO}_2 ), mmHg (range)</td>
<td>44.3 (36.3-51.5)</td>
<td>40.2 (38.0-42.0)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, unless otherwise specified. BMI refers to body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; RDI, respiratory disturbance index; SaO₂, oxygen saturation; t90, time of oxygen saturation below 90% during total sleep time; REM, rapid eye movement sleep.

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**Table 2**—Transcranial Magnetic Stimulations Data in Patients with Obstructive Sleep Apnea Syndrome and Controls

<table>
<thead>
<tr>
<th>Data</th>
<th>Value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSAS</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>ALMEP, ms</td>
<td>20.9±0.8</td>
<td>20.6±1.2</td>
</tr>
<tr>
<td>CMTT, ms</td>
<td>5.7±0.7</td>
<td>6.0±0.4</td>
</tr>
<tr>
<td>CMAP/MEP, %</td>
<td>29.7±8.6</td>
<td>41.9±19.6</td>
</tr>
<tr>
<td>RMT</td>
<td>47.5±13.9</td>
<td>40.5±7.2</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. ALMEP refers to absolute latency of motor evoked potential; CMTT: central motor transmission time; CMAP/MEP: compound motor action potential / motor evoked potential; RMT: relaxed motor threshold.

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**Figure 1**—Study design. After a nocturnal polysomnography (nPSG) at 10 AM subjects underwent Transcranial Magnetic Stimulation (TMS), and arterial blood gas measurements. TMS was then repeated other four time in the following hours. Definition of abbreviations: ESS = Epworth sleepiness scale; MEP = motor evoked potential; SSS = Stanford sleepiness scale; RMT = resting motor threshold; CSP = cortical silent period.
controls did reach statistical significance only at 10 AM for 130% RMT intensity.

Compared to the controls, the patients with OSAS, showed, at 10 am, a significant positive correlation between PaCO₂ and duration of CSP (the higher the PaCO₂ values, the higher the CSP duration) elicited with stimulus intensity of 95% RMT (P < .05; r=0.74) (Figure 4). A similar finding was found for CSP obtained with the stimulus intensity of 100% RMT (P < .01; r=0.79) and 105% RMT (P < .01; r=0.76). A significant negative correlation was found between PaO₂ and duration of CSP elicited with a stimulus intensity of 95% RMT (P < .01; r=0.77) at 10 AM.

Neither patients nor controls exhibited significant relationships between the TMS parameters and sleep stages, sleepiness, and nocturnal and morning respiration data. Moreover, no correlation was found between TMS parameters, respiratory disturbance index, and arousal index.

DISCUSSION

The main finding of this study is the evidence of alterations in motor cortical excitability in awake OSAS patients, in which the CSP is longer. This increment is related to the intensity of stimulation: CSP was longer with lower-intensity stimuli (95% RMT, 100% RMT, 105% RMT) at almost all recording times, but, with greater TMS stimuli, the CSP was longer only in the morning. Only 2 studies have dealt with TMS in OSAS. In a preliminary report, Cegla and Frode showed that latencies of the MEPs in hand muscles are longer in OSAS than normal controls, suggesting some widespread defect in the conductivity or excitability of the system. These findings were not confirmed in our results nor...
Our study, showing a recent paper.

In line with a previous study of Civardi et al., we confirm alterations of motor cortical excitability in awake OSAS patients who have a longer CSP. The novel finding of this study is the relationship between the prolongation of CSP duration and the intensity of stimulation and the time of recording: CSP is longer with low-intensity stimulation (95% RMT, 100% RMT, 105% RMT) at all recording times, but, with greater TMS stimuli, patients showed longer CSP only in the morning.

The length of late CSP is meant to reflect complex motor cortical inhibitory phenomena possibly linked to the GABAergic tone. The silent period is prolonged in many pathologic conditions, such as Huntington disease, or in the motor cortex in epileptic patients. Invariably, authors interpret these findings as the result of an imbalance of cortical excitability toward a state of enhanced inhibition. We applied this view to explain the prolonged CSP of OSAS patients while awake. Many factors may contribute to changes in cortical excitability in our patients. First of all, the cortical-excitability adjustments related to the neural basis of sleepiness are per se caused by sleep disruption. Manganotti et al. have studied the effect of sleep deprivation in normal subjects. They found that the level of subjective sleepiness during the night was associated with an increase in both motor threshold and duration of the silent period; both parameters returned to baseline values in the morning when subjective sleepiness was highest. In addition, Civardi and colleagues found no significant changes in the CSP and threshold to stimulation after sleep deprivation. In our study, the sleep disruption of OSAS patients caused an increase in their sleepiness, as indicated by the Stanford Sleepiness Score. The analysis of variance for repeated measures revealed that the changes in TMS parameters did not follow a circadian rhythm. Indeed, with lower TMS intensity (95% RMT, 100% RMT, 105% RMT) stimulus intensity at 10 am and PaCO₂, CSP durations returned to basal values, indicates that nocturnal desaturation and alteration of cortical excitability are independent factors in OSAS patients.

The last factor is the increase of PaCO₂. Priori and colleagues found that a significant reduction of CSP duration was associated with a reduction of end-tidal PaCO₂ after 10 minutes of hyperventilation in a group of healthy subjects. Fifteen minutes after hyperventilation, both PaCO₂ and CSP durations returned to basal values. Furthermore, Placidi et al. attributed the morning changes in cerebral vasoreactivity to the nocturnal increase of PaCO₂ in OSAS patients. Cerebral vasoreactivity significantly decreased in the afternoon, though it remained higher than in controls. In keep-

**Table 3—Duration of the Cortical Silent Period in Patients with Obstructive Sleep Apnea Syndrome and Control Subjects**

<table>
<thead>
<tr>
<th>Time</th>
<th>Control (Mean ± SD)</th>
<th>OSAS (Mean ± SD)</th>
<th>Time</th>
<th>Control (Mean ± SD)</th>
<th>OSAS (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 AM</td>
<td>70.9±15.3</td>
<td>106.5±11.4</td>
<td>12 AM</td>
<td>80.3±10.4</td>
<td>113.9±26.3</td>
</tr>
<tr>
<td>100</td>
<td>104.5±32.6</td>
<td>135.9±19.4</td>
<td>105</td>
<td>139.2±31.9</td>
<td>169.1±20.6</td>
</tr>
<tr>
<td>130</td>
<td>178.9±27.3</td>
<td>204.9±20.2</td>
<td>150</td>
<td>213.3±31.9</td>
<td>232.4±29.6</td>
</tr>
<tr>
<td>150</td>
<td>70.9±15.3</td>
<td>106.5±11.4</td>
<td>12 AM</td>
<td>80.3±10.4</td>
<td>113.9±26.3</td>
</tr>
<tr>
<td>100</td>
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<td>150</td>
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<td>232.4±29.6</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. RMT refers to rest motor threshold; OSAS: obstructive sleep apnea syndrome.

In a recent paper, in a previous study of Civardi et al., we confirm alterations of motor cortical excitability in awake OSAS patients who have a longer CSP. The novel finding of this study is the relationship between the prolongation of CSP duration and the intensity of stimulation and the time of recording: CSP is longer with low-intensity stimulation (95% RMT, 100% RMT, 105% RMT) at all recording times, but, with greater TMS stimuli, patients showed longer CSP only in the morning.

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**Figure 4—Correlation between values of duration of CSP elicited at 95% RMT stimulus intensity at 10 am and PaCO₂ resting values in OSAS patients (A) and controls (B).**
During apneic episodes, upper airway muscle dysfunction might be involved in upper airway muscle dysfunction. The lower activity of upper airway muscles might be linked to the changes in CSP, actually lead to sleep-related motor suppression of pharyngeal muscle activity remains a matter of speculation.

The enhanced motor cortical inhibition we show in awake OSAS patients is another electrophysiologic marker of central nervous system involvement, in addition to dysfunction of cortical associative area, as assessed by means of event-related potentials. The PaCO2 levels could affect the function of excitatory and inhibitory cortical circuits. Further studies are, however, needed to verify the reversibility of these alterations with treatment (e.g., continuous positive airway pressure) and to show at what level of the intracortical circuits these modifications take place.

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