Deficits in involuntary attention switching in obstructive sleep apnea syndrome

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Received 31 March 2006; received in revised form 4 May 2006; accepted 19 August 2006

Abstract

Cognitive functions are altered in patients with obstructive sleep apnea syndrome (OSAS) and it has been proposed that vigilance and attentional deficits play a pivotal role in all aspects of these deficits. One way to assess attentional system integrity is the study of event-related-potentials (ERP), but only a few ERP studies have been conducted in patients with OSAS. The aim of the study was to use ERP to further assess attentional impairments in these patients. Thirteen OSAS patients and 13 age-matched controls underwent a night of polysomnographic recording. Each subject was also tested with an ERP paradigm where standard (95%, 1000 Hz), high deviant (2.5%, 1250 Hz) and low deviant (2.5%, 1050 Hz) tones were presented. Subjects were asked to ignore the stimuli and read during the task. Mismatch negativity (MMN) and P3a amplitudes and latencies were measured. No between-group difference was observed for sleep stages, except a lower percentage of rapid eye movement (REM) sleep in patients with OSAS (p < 0.01). Moreover, the OSAS group showed a higher micro-arousal index and more sleep transitions than the control group (p < 0.05). A significant group effect was found for the amplitude of the P3a component (p < 0.05) that was lower in patients with OSAS for both high and low deviant tones. No between-group difference was found for the MMN and the P3a latencies. In conclusion, patients with OSAS have specific alterations of the P3a component that reflects involuntary attention switching, but automatic auditory processing assessed by MMN appears to be preserved.

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Keywords: Obstructive sleep apnea syndrome (OSAS); Event-related potentials (ERP); Involuntary attention switching; Mismatch negativity (MMN); P3a

Obstructive sleep apnea syndrome (OSAS) is a common sleep-related breathing disorder attributed to the upper airway obstruction and characterized by apneas or hypopneas leading to recurrent hypoxemia, hypercapnia, increased ventilatory efforts and sleep disruption. OSAS is associated with diurnal symptoms such as excessive daytime sleepiness [12], decreased daytime vigilance [5] and cognitive deficits such as alteration of selective and sustained attention [20,26], memory impairments [23] and executive function deficits [22,29]. These cognitive deficits observed in OSAS can be largely explained by an alteration in the functioning of the prefrontal cortex, which is sensitive to both transient nocturnal hypoxemia and sleep disruption [6].

Event-related-potentials (ERP) are sensitive to attentional deficits and abnormal ERP have been previously reported [13,18,27,30,31,35,36]. This technique represents the averaged EEG signal recorded following the presentation of stimuli and allows the measurement of pre-attentional and attentional information processing. All ERP studies performed in OSAS patients so far used tasks in which subjects have to pay attention to the stimulus presentation, but no study investigated the automatic brain response associated with deviant stimuli during an inattentive condition.

The main ERP component associated with the information processing during a passive or inattentive task is the mismatch negativity (MMN). The MMN is a brain response elicited when an acoustic change occurs (e.g., change in frequency, intensity, duration, location, etc.) in a sequence of repeated tones [21]. The recurrent tone, or standard stimulus, forms a stable memory trace across trials and the occurrence of a deviant tone generates a different pattern of brain activity, the MMN. This negative ERP
component appears approximately 100–250 ms after the stimulus deviance and the particularity of this response is that no attention or behavioral response is required by the subject to be elicited. This component represents the automatic detection of acoustic changes and the initiation of an attentional switch. If a stimulus is sufficiently deviant from the standard one, the MMN is followed by the P3a, which peaks approximately 250–400 ms after the deviant stimulus onset [9,17,32]. While the MMN is associated with the initiation of the attentional switch, the P3a is the sign of the involuntary capture of attention by the deviant sound. The P3a is characterized by a fronto-central scalp distribution and a drastic reduction in the amplitude of this component was observed in patients with prefrontal lesions [15].

All ERP studies conducted in patients with OSAS used tasks in which fully volitional attention is required, as it is the case during neuropsychological testing. However, no study has investigated the information processing during an inattentive condition, which is represented by MMN and P3a components. In order to understand the attentional deficits observed in OSAS patients, it is necessary to evaluate the integrity of the automatic and the pre-attentional systems that may have an impact on the later volitional attention and behavioral response. The aim of the present study was thus to better characterize the electrophysiological, and hence the early attentional deficits of patients with OSAS, within the context of an inattentive task.

Thirteen patients with an obstructive sleep apnea index (SAI) greater than 10 per hour of sleep were included in the study and were compared to 13 normal controls matched for age and gender. Control subjects had no history or sleep laboratory evidence of sleep apnea syndrome (defined as an AHI greater than five). Exclusion criteria for both groups were the presence of a neurological, psychiatric or pulmonary disease or an intake of drugs known to affect sleep, daytime vigilance or cognition such as antidepressants, hypnotics and benzodiazepines. Since high blood pressure is a common feature in patients with OSAS, only patients with unstable high blood pressure were excluded.

All subjects completed the Epworth Sleepiness Scale (ESS) [14] and underwent an auditory examination performed by an audiologist. None of the subjects included in the present study showed any auditory deficit in the frequency bands used in the ERP paradigm. Each participant was informed of the research protocol and gave written informed consent before the beginning of the study. The protocol was approved by the University-Hospital ethics committee.

All subjects were recorded for one night in the sleep laboratory. Polysomnographic recording was performed using four EEG derivations (C3, C4, O1, O2) referred to linked earlobes, electrooculograms (EOG) and chin electromyogram. Sleep stages were scored according to the standard method developed by Rechtschaffen and Kales [25]. Thoracoabdominal plethysmograph and oro-nasal canula were used to monitor respiration and transcutaneous finger pulse oximeter was used to measure oxygen saturation. An apnea was defined as a total cessation of airflow lasting at least 10 s and a hypopnea was scored as a reduction of airflow of at least 50% from baseline, lasting at least 10 s [3]. Moreover, hypopneas with a decrease in oxygen saturation greater than 4% were also identified. Sleep efficiency was defined as time spent asleep over the entire duration of sleep period.

All subjects were tested between 8:00 and 9:30 a.m. using an ERP auditory paradigm, which consisted in the presentation of standard (1000 Hz), high deviant (1250 Hz), and low deviant (1050 Hz) tones by insert earphones. The standard stimulus appeared in 95% of the trials, whereas each deviant stimulus appeared in 2.5% of the trials. The interstimulus interval varied randomly between 400 and 600 ms and the tone intensity was 70 dB SPL. A total of 1400 stimuli were presented during 12 min. Subjects were asked to ignore the sounds and to read during the recording. Constant EEG and visual monitoring was done in order to ensure that subjects were not transiently falling asleep during the task.

The EEG was recorded from 23 electrodes (Fz, F3, F4, F7, F8, FCz, FC3, FC4, Cz, C3, C4, T7, T8, TP7, TP8, Pz, P3, P4, P7, P8, Oz, O1, O2) placed according to the guideline for standard electrode position [8]. All electrodes were referred to the nose and EOG was also recorded. The filter band-pass was 0.01–40 Hz and the EEG were digitized at 256 Hz with a 100 ms prestimulus baseline. Stimulus presentation and EEG recording were done with Neuroscan system (Neurosoft Inc., Sterling, USA).

Trials on which EEG changes exceeded ±60 μV was rejected automatically for the ERP analysis. An EOG artifact correction was applied through the Neuroscan software. The EEG was averaged time-locked to the stimulus for each type of stimuli and this resulted in three average waveforms: standard stimuli (1000 Hz), high deviant stimuli (1250 Hz) and low deviant stimuli (1050 Hz). Additional filters (0.01–20 Hz, 12 dB/octave) were applied on average ERP waveforms. The standard waveform was subtracted from each deviant waveform and these subtractions lead to two average signals (high deviant tone minus standard tone; low deviant tone minus standard tone) from which MMN and P3a have been measured. Amplitude was measured relative to the mean of the prestimulus baseline. Latencies and amplitudes of the highest negative peaks were measured in the 100–250 ms latency window for MMN for 12 electrodes (Fz, F3, F4, FCz, FC3, FC4, Cz, C3, C4, Pz, P3, P4). Inversion of polarity in temporal electrodes served for the identification of MMN. The P3a was defined as the highest positive peak measured in the 250–400 ms latency window for the same 12 electrodes. Amplitudes and latencies measured for these electrodes were averaged in order to obtain the four following regions: frontal (Fz, F3, and F4), fronto-central (FCz, FC3, and FC4), central (Cz, C3, and C4) and parietal (Pz, P3, and P4) regions.

Between-group differences on demographic and polysomnographic variables were assessed using student t-tests. Latencies and amplitudes for MMN and P3a components were analyzed with three-way ANOVAs with one independent factor (GROUP) and two repeated measures (TONES: high deviant and low deviant; REGION: frontal, fronto-central, central and parietal). A Greenhouse-Geisser correction for sphericity was applied to all repeated measures. When ANOVAs showed significant main effects, Tukey HSD tests were used for post-hoc comparisons. Pearson correlation coefficients were used to measure the relationships between polysomnographic
variables and ERP characteristics. Since there were multiple analyses, correlations were considered significant if \( p < 0.01 \).

Table 1 shows demographic and polysomnographic data for patients with OSAS and control subjects. Oxygen saturation was not analyzed in one patient with OSAS and one control subject due to technical problems. No between-group difference was observed for education level. On the other hand, OSAS patients presented a greater body mass index and higher ESS scores than control subjects. No between-group difference was observed for demographic variables in fronto-central and central regions than in the parietal region (\( p < 0.01 \) in both cases). No GROUP difference was observed for MMN amplitude.

**MMN latency:** A significant TONE by REGION interaction was found (\( F(3, 72) = 6.63, p < 0.01, \varepsilon = 0.556 \)) and post-hoc comparisons showed prolonged latencies for the low deviant tone in comparison with the high deviant tone in frontal (\( p < 0.01 \)) and fronto-central (\( p < 0.05 \)) regions, but not in the other regions. No GROUP difference was found for MMN latency.

**P3a amplitude:** A significant GROUP effect was observed for P3a amplitude (\( F(1, 24) = 4.62, p < 0.05 \)) and was characterized by a reduced P3a amplitude in the OSAS group in comparison with the control group. A TONE effect was also found (\( F(1, 24) = 10.90, p < 0.01 \)) and, as it was observed for MMN amplitude, high deviant tone showed greater P3a amplitude than the low deviant tone. A REGION effect was also found (\( F(3, 72) = 6.32, p < 0.05, \varepsilon = 0.38 \)) and was characterized by higher MMN amplitudes in fronto-central and central regions than in the parietal region (\( p < 0.01 \) in both cases). No GROUP difference was observed for MMN amplitude.

**P3a latency:** A significant TONE by REGION interaction was found (\( F(3, 72) = 5.62, p < 0.05, \varepsilon = 0.48 \)) and was characterized by a shorter P3a latency in frontal and fronto-central regions for the high deviant tone in comparison with the low deviant tone (\( p < 0.01 \) in both cases). As it was the case for MMN latency, no GROUP effect was observed for P3a latency.

The aim of the study was to examine MMN and P3a characteristics in patients with OSAS in order to assess the integrity of early attentional processes in this population. Our results indicate a reduction in the P3a amplitude in these patients in
Fig. 1. Subtracted grand-average waveforms for the high deviant tone in patients with OSAS (grey line) and control subjects (black line). 

Fig. 2. Subtracted grand-average waveforms for the low deviant tone in patients with OSAS (grey line) and control subjects (black line).

comparison with control subjects, while no significant change was found for the MMN. This reduction in P3a amplitude was not influenced by the magnitude of the tone deviance. The P3a has been associated with involuntary orientation of attention toward a deviant sound and this automatic process occurs even if the subject does not pay attention to the stimuli. The diminution of the P3a amplitude observed in OSAS patients probably reflects a reduction of the cognitive resources allocated to detect changes occurring in the auditory environment.

Recent neuroimaging studies showed anomalies in patients with OSAS characterized by a loss in gray matter in various brain regions including the lateral prefrontal cortex, the anterior...
cingulate, the temporal lobe and the hippocampus [19] and by a functional disturbance of the lateral prefrontal cortex [33]. The differential impact of OSAS on the MMN and the P3a may be partially explained by the fact that these ERP components have different brain generators and they are thus differently affected by these structural and functional changes. The P3a, which is generated by a widespread network of brain regions such as the dorsolateral prefrontal cortex [15], the superior temporal plane [2], the hippocampus [16] and the anterior cingulate [4], is more affected by the structural and the functional alterations found in OSAS in comparison with the MMN, which is generated by the supratemporal cortex and by the inferior frontal gyrus [1,7,10,24].

Our results obtained on MMN and P3a are similar to those recently found in normal subjects in different sleep conditions. Salmi et al. [28] investigated the impact of sleep quality on ERP and they showed that the MMN was insensitive to sleep quality variations, while the P3a amplitude was significantly correlated with sleep efficiency. The effect of total sleep deprivation on the variations, while the P3a amplitude was significantly correlated and they showed that the MMN was insensitive to sleep quality [1,7,10,24].

The ERP latency represents the information processing speed and in the present study, no between-group difference was found for either MMN or P3a latencies. Some previous studies have shown increased reaction times (RT) in patients with OSAS [5,34]. RT may be determined by several information processing stages such as stimulus detection, attention orientation, stimulus classification, response choice and motor response execution. Our results allow us to suggest that the stimulus detection speed is normal in OSAS and cannot explain the abnormal RT observed in some previous studies. However, the increased RT could be explained by impairment in involuntary attention switching to the target stimulus.

In conclusion, the involuntary attentional switching system is altered in OSAS as revealed by P3a anomalies. This deficit may interfere with almost all cognitive functions and can explain part of the frontal deficits observed in previous neuropsychological studies in this population. More studies are needed to evaluate the exact impact of this involuntary orientation problem on selective and divided attention and on other cognitive functions.

Acknowledgements

This research was supported by the Canadian Institutes of Health Research (grant to J.M. and studentship to N.G.), by the Fonds de la Recherche en Santé du Québec (studentship to N.G.), and by ANTADIR (studentship to S.M.). J.M. currently holds a Canadian Government Chair on Sleep Disorders. The authors are grateful to Jean Paquet, Ph.D., for helping with statistics and Dominique Petit, Ph.D., for reviewing the manuscript. The authors also thank Mireille Charron and Benoît Adam for their technical assistance.

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