Possible effect of the trigeminal nerve stimulation on auditory event-related potentials

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Abstract— Trigeminal input to noradrenergic Locus Coeruleus (LC) neurons is important for the maintenance of arousal and may boost cognitive performance. Since it has been shown that LC enhances discrimination of acoustic stimuli and the associated electroencephalographic (EEG) waves, such as event related potentials (ERPs) P300, we set a protocol aimed to verify whether trigeminal nerve stimulation (TNS) may be utilized for improving acoustic discrimination of different tones. In two separate experiments, we evaluated P300 ERPs elicited by an acoustic oddball paradigm performed before and after TNS or sham-TNS, respectively. The ultimate purpose of this evaluation is to verify whether it is possible to exploit TNS as a treatment in subjects with disorders of consciousness.

I. Introduction

Trigeminal afferents play a particularly important role in the control of arousal/alertness and attention through their connections with structures belonging to the Ascending Reticular Activating System (ARAS) [1]. Trigeminal primary and/or secondary neurons project to the pontomedullary reticular formation, to the cholinergic pedunculopontine and the laterodorsal tegmental nuclei, to the histaminergic tuberomammillaryand to the noradrenergic locus coeruleus (LC) neurons. Projections to the LC arise in part from muscle spindles afferents localized in the trigeminal mesencephalic nucleus [2]. LC neurons, in turn, are able to affect vigilance via their mainly ipsilateral projections to cortical regions [3], leading to an improvement of cognitive performance [4], to a change in the coupling between cerebral regions [5] which is related to awareness [6] and to an enhancement of the P300 wave elicited by sensory discrimination [7].
To investigate whether trigeminal nerve stimulation (TNS) could be exploited in the treatment of disorders of consciousness we set up a protocol for investigating its effects on the P300 elicited by an acoustic oddball paradigm.

II. Material and Methods

Subjects. 2 Subjects (healthy volunteers without neurological or psychiatric disorders, females, 28 years) were enrolled in this study. The experimental procedure consisted of two 20-minutes auditory oddball tasks, respectively before and after either a TNS (first subject) or sham-TNS (second subject). A random sequence of frequent standard tones (n=400) and rare oddball tones (n=100) was presented. The subjects were instructed to count the rare tones.

Trigeminal nerve stimulation (TNS). TNS consisted of 10 minutes of transcutaneous stimulation of the trigeminal motor branches. Biphasic (cathodal/anodal) current pulses (0.54ms duration, 21-25mA intensity) were delivered by two stimulators through couples of electrodes applied at the level of incisura sigmoidea and of the submental region of both sides. Stimuli at 0.618 Hz and 40 Hz were utilized for elevator and depressor muscles, respectively. In this way, elevators alternated contraction and relaxation, while depressor muscles were tonically contracted, giving rise to small amplitude mandibular movements (1 mm).The intensity of the right and left current was adjusted to obtain an asymmetrical response of the masseter muscles on both sides.

Sham-TNS. In the sham-TNS condition, electrodes were applied but no stimulation was given.

Electrophysiological Recordings and EEG Data Analysis. EEG data were acquired at a sampling rate of 1024 Hz using 20 electrodes, affixed with electrode paste and tape on the scalp and positioned according to the 10–20 International Electrodes Placement System. The reference was placed on the mastoid. Data were analyzed via custom routines based on EEGLAB toolbox [8] and Matlab R2017b. Continuous EEG signals were band-pass filtered (0.5Hz-30Hz) and re-referenced to T5. The EEG was segmented into epochs time locked to [−0.5 1]s with respect to the onset of the stimuli and the baseline value [-0.5 0]s was subtracted from each trial. Epochs with prominent artifacts were then removed by visual inspection and stereotyped muscle and ocular artifacts were removed by Independent Component Analysis (ICA) [9]. Processed epochs were averaged separately for standard and target stimuli and for pre- and post- stimulation phases respectively.

Statistical Analysis. For each subject, differences in P300 amplitude between pre- and post- stimulation periods were analyzed by evaluating for each single trial the trace amplitude at the time of the P300 peak observed in the average recordings (Fig.1) and by comparing them by an independent t-test (significance α=0.05).

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III. Results

Fig. 1a shows the P300 amplitude elicited by rare tones in FZ, CZ and PZ electrodes before and after TNS/sham-TNS respectively. The P300 amplitude was not modified by TNS, while it significantly decreased following sham-TNS ($p<0.05$ at all electrodes) (Fig. 1b).

Fig. 1. (a) Auditory event-related potentials (ERPs) averaged over Fz, Cz and Pz before and after TNS/sham-TNS. (b) Comparison of ERP responses to the rare tones recorded before and after TNS/sham-TNS stimulation at Fz, Cz and Pz electrodes

IV. Discussion

This experiment allowed to assess, in individual subjects, the significance of the changes elicited in the P300 amplitude by TNS and sham-TNS. The P300 undergoes a significant spontaneous decay with the sham-TNS. On the contrary, the P300 amplitude is comparable following TNS. It is possible to speculate that the TNS potentially modulates ARAS structures, in particular LC, and contributes to maintaining attentive resources at high alertness levels.

V. Conclusion

These preliminary observations indicate that it is possible to evaluate in individual subject the effect of TNS on an auditory oddball paradigm, thus verifying the opportunity of its use as a treatment for improving awareness in disorders of consciousness.

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