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Mismatch Negativity in essential tremor: Role of age at onset in pre-attentive auditory discrimination

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HIGHLIGHTS

- Pre-attentive auditory discrimination was studied in essential tremor (ET) patients.
- MMN latency is prolonged in elderly-onset patients while in young-onset patients is not.
- This data supports the hypothesis that ET represents a heterogeneous family of diseases.

ABSTRACT

Objective: To investigate whether pre-attentive auditory discrimination is impaired in patients with essential tremor (ET) and to evaluate the role of age at onset in this function.
Methods: Seventeen non-demented patients with ET and seventeen age- and sex-matched healthy controls underwent an EEG recording during a classical auditory MMN paradigm.
Results: MMN latency was significantly prolonged in patients with elderly-onset ET (>65 years) ($p = 0.046$), while no differences emerged in either latency or amplitude between young-onset ET patients and controls.
Conclusions: This study represents a tentative indication of a dysfunction of auditory automatic change detection in elderly-onset ET patients, pointing to a selective attentive deficit in this subgroup of ET patients.
Significance: The delay in pre-attentive auditory discrimination, which affects elderly-onset ET patients alone, further supports the hypothesis that ET represents a heterogeneous family of diseases united by tremor; these diseases are characterized by cognitive differences that may range from a disturbance in a selective cognitive function, such as the automatic part of the orienting response, to more widespread and complex cognitive dysfunctions.

1. Introduction

Essential tremor (ET), which is clinically characterized by an 8- to 12-Hz kinetic tremor of the arms and is often accompanied by head and voice tremors, represents the most common pathological tremor in humans (Louis, 2009). However, patients with essential tremor have been shown to experience cognitive deficits, which are typically mild but progressive. This suggests that the clinical picture of ET is much broader than has previously been believed and that it might be more appropriate to consider ET as a neurodegenerative disorder (Benito-León and Louis, 2006; Bermejo-Pareja, 2011).

The cognitive features of ET, which were first reported in 2001 (Lombardi et al., 2001) and have been repeatedly described since then (Gasparini et al., 2001; Troster et al., 2002; Lacritz et al. 2002; Sahin et al., 2006), include clinically subtle attentional and executive dysfunctions, such as deficits in tests of verbal fluency, naming, mental set-shifting, verbal and working memory, complex auditory attention, visual attention and response inhibition (Lorenz and Deuschl, 2007), all of which are likely to reflect difficulties in initiating and maintaining information processing strategies (Louis, 2010).

Attentional functioning in ET has previously been explored mainly by means of neuropsychological and neuroimaging studies (Cerasa et al., 2010; Passamonti et al., 2011). However, cognitive operations linked to a mental or a physical event are well reflected by some components of event-related potentials (ERPs), which may, given their exceptional temporal resolution, represent a reli-

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able tool for obtaining information on how the brain processes signals without any motor interference (Duncan et al., 2009).

Information processing in ET has been investigated by means of ERPs in previous studies (Antal et al., 2000; Balaban et al., 2012; Pauletti et al., 2013), including a recent one in which the presence of a peculiar attentional deficit that is related to the evaluation of novelty and is part of conscious aspects of the orienting response was described (Pauletti et al., 2013).

By contrast, the automatic pre-attentive part of the orienting response to an acoustic change that may lead to an attention switching process has not yet been investigated.

Within ERPs, the Mismatch Negativity (MMN) is believed to represent the automatic process that detects a difference between an incoming stimulus and the sensory memory trace of preceding stimuli (Duncan et al., 2009). The MMN is elicited, in fact, when the auditory input does not match the actual or predicted sensory information encoded in this trace, even when the subject is not attending to the stimuli (Näätänen et al., 2011).

The MMN response is a negative displacement in the difference wave obtained by subtracting the ERP to frequent, standard stimuli from that to deviant stimuli at the frontocentral sites (Duncan et al., 2009). The recording of this component, whose biological function is to monitor and detect any change in the ongoing auditory stimulation irrespective of where the subject's attention is focused, offers an insight into the attentional processes that govern the access of auditory input to conscious perception and higher forms of memory (Näätänen et al., 2007; Duncan et al., 2009).

It thus represents an effective means of examining aspects of attention and cognitive processing that have not yet been investigated in patients with ET.

Following reports that ET patients may experience cognitive deficits, an association of elderly-onset ET and dementia has also recently been described. (Benito-León et al., 2006; Bermejo-Pareja et al., 2007; Thawani et al., 2009; Louis et al., 2010). Age at onset in ET remains a matter of debate, as it is still unclear whether elderly-onset ET subjects are, or are not, a group with a distinct disease entity (Louis, 2013).

The aims of our study were to investigate whether pre-attentive auditory discrimination is impaired in non-demented patients with ET and to explore its relationship with age at onset of ET.

2. Subjects and methods

2.1. Subjects

Seventeen outpatients (5 males, 12 females; 68.2 ± 12.4 years), with a diagnosis of ET according to the Consensus Statement of the Movement Disorder Society on Tremor (Deuschl et al., 1998), were consecutively recruited for the study at our clinic from March 2011 to March 2012.

All the patients were examined by two independent experienced neurologists and were clinically evaluated by means of the Fahn Tolosa Marin rating Scale (FTM-RS) (Fahn et al., 1993).

The main clinical characteristics of the ET population are shown in Table 1. No patient was under medication at the time of the study.

Seventeen healthy age- and sex-matched volunteers (5 males, 12 females; mean age 67.6 ± 12.4 years), with unremarkable personal and family histories for psychiatric and neurological disorders and no abnormalities at the neurological examination, were consecutively recruited from non-consanguineous relatives of neurological outpatients as the control group in the same period. None of the controls was taking any medication.

All the subjects enrolled in the study underwent a Mini-Mental State Examination to rule out the presence of dementia. All the participants were right-handed and gave their written informed consent to the study.

2.2. Psychophysiological evaluation

2.2.1. Paradigm

All the participants underwent a single deviant MMN paradigm.

The task consisted of an ongoing oddball sequence of repeated standard sounds of 1000 Hz, occasionally interrupted by rare deviant sounds of 1100 Hz with a probability of 0.1. Two consecutive blocks of stimuli, each including 500 stimuli and lasting approximately ten minutes, were administered in the same recording session. Each stimulus consisted of 150 ms duration with 5 ms rise and fall time. The sound level was 80 dB and the inter-stimulus interval was set at 1 s. The sequence was randomized at the run time, the only constraint being that at least two standard stimuli were always presented between each deviant stimulus.

The sounds were presented and controlled by a PC running system. We opted for a relatively long inter-stimulus interval and a salient deviance, given the demographic and clinical characteristics of the sample in study.

The subjects were not informed of the occurrence of two different tones and were instructed to distract themselves by watching a subtitled video (sound off).

2.3. EEG recording

Participants were seated in a comfortable chair in a sound-attenuated room. During recordings, subjects were instructed to minimize blinking and reduce eye movements as much as possible. The electrophysiological signals were recorded by means of Ag/AgCl electrodes fixed on the scalp. Active electrodes were placed at the F3, Fz, F4, C3, Cz, C4, P3, Pz and P4 sites, according to the International 10–20 System and two additional electrodes were placed on the left and right mastoids, referred to the nose. A Mizar Sirius EEG-EP amplifier was used. The bipolar electro-oculogram (EOG) was recorded from above and below the left eye. All inter-electrode impedances were maintained below 5 kΩ. Brain electric activity and EOG were filtered using a 0.1–30 Hz bandpass (sampling rate 500 Hz). A notch filter was also applied. The data were digitized with an analog/digital (A/D) converter at a sampling rate of 1024 Hz and stored on a hard disk.

2.4. ERP analysis

Trials containing eye movements (including blinks) were automatically rejected online, according to guidelines (Duncan et al., 2009). A further selection was performed in the offline analysis to reject other kinds of artifacts not detected by the automatic rejection procedure.

The ERPs were obtained by averaging EEG epochs separately for all deviant and standard tones. The analysis epoch was of 600 ms with a 100 ms prestimulus baseline. The ERPs were digitally bandpass filtered at 1–20 Hz. Difference waveforms were calculated by subtracting the ERP of standard stimuli from those elicited by the deviant stimuli.

The distribution of the MMN across the active scalp electrodes was used to verify that the response observed was maximal over frontal sites, and as expected, the MMN showed a distribution of frontal negativity. Therefore, MMN latency and amplitude were manually determined by investigators who were blind to group status, from the most negative peak occurring at 100–250 ms post stimulus-onset at Fz on the difference wave with a bandpass narrowed to 2–10 Hz (Tervaniemi 1999), being aware that, for each subject, the window of analysis started just after the mean peak latency for the N1 peak of the standard stimulus.