An exploratory study on the use of event-related potentials as an objective measure of auditory processing and therapy effect in patients with tinnitus : a transcranial direct current stimulation study

Reference:
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Abstract

Objective: Treatment effect in tinnitus research is commonly evaluated by use of self-report questionnaires. As this is a solely subjective assessment method, the need for an objective measurement is paramount to genuinely evaluate the effects of therapeutic interventions. The current study explores the value of event-related potentials (ERPs) in the evaluation of high-definition transcranial direct current stimulation (HD-tDCS) for tinnitus treatment.

Study Design: Prospective exploratory study

Setting: Tertiary referral center

Patients: 22 chronic tinnitus patients

Intervention: HD-tDCS

Main outcome Measures: ERPs

Results: The results show a significant shortening of the N1, P2, N2 and P3 latencies after HD-tDCS treatment. Moreover, the increased amplitude of the P2 and N2 peaks result in more salient and clear peaks, with the amplitude of N2 being significant larger after HD-tDCS. However, the ERP changes are not significantly correlated with the change in TFI total score.

Conclusions: The current study was the first to explore ERPs as objective measure in a study with HD-tDCS in tinnitus patients. Adding ERPs to the outcome measures in tinnitus research may lead to a better understanding of the therapeutic effect in the future. The results showed a shortening of ERP latencies and an increased N2 amplitude, possibly reflecting more effective sound processing with higher recruitment of synchronized neurons in the auditory cortex. Future studies should elaborate on these results, by collecting control data and adding a sham group, to provide a better insight in the underlying mechanism of the ERP changes after tinnitus treatment.

Introduction

In normal-hearing individuals, a series of sound waves transformations occurs during auditory processing from the external ear to the auditory cortex. In order to consciously perceive a sound, bottom-up (incoming data-based) and top-down (prior knowledge-based) processes have to co-act (1). Deafferentation of central auditory structures by disruptions along the auditory pathway leads to several neural changes that underlie tinnitus (2,3). Tinnitus is defined as the conscious perception of a sound (e.g. hissing, sizzling or ringing) in the absence of an external sound source (4). It is hypothesized that tinnitus results from maladaptive plastic changes involving a wide network of these cortical areas and subcortical structures (5), yet the precise pathophysiologic mechanism is not fully understood (4). As 2.4% of the population experiences a severely negative impact of the tinnitus on the quality of life (4,6), there is a high need to investigate this disruption along the auditory pathway to optimize current treatments.

Auditory evoked potentials (AEPs) objectively measure auditory processing by recording neural activity elicited by external sounds. More precisely, when these stimuli are specific events, these potentials are described as event-related potentials (ERPs). ERPs provide insight into brain processing and, when recorded with multi-channel systems, display the brain functionality and connection between different brain areas. ERP latencies are considered to represent the time course of auditory and cognitive processes (e.g. evaluation of a stimulus and selection and preparation of an appropriate response), whereas ERP amplitudes are related to the amount of synchronized neuronal activity and its location (7). As ERPs provide insight into these brain processes, they might offer an objective measurement of sound processing in tinnitus.

As such, there is a growing body of literature that indicates distorted ERPs in tinnitus patients. ERPs can be divided according to peak latencies in P1, N1, P2, N2 and P3. The P1 component, occurring approximately 50-100 milliseconds (ms) post-stimulus, is involved in sensory gating and thus reflects an individual's ability to filter irrelevant information (8). Since this component does not differ between tinnitus patients and controls, level of arousal or habituation to repetitive stimulation may be similar in those two groups (9). The N1 component, occurring approximately 100ms post-stimulus, is primarily determined by sensory processing (10) and is considered to reflect the recognition of stimuli rather than differences between stimuli (11). This ERP component has been conceptualized as the physiological correlate of both attentional (10,12) and working memory operations (13). It has been shown that N1 latency is increased and N1 amplitude is reduced in tinnitus patients (1,14). The P2 component, occurring approximately 200-250ms post-stimulus, is thought to reflect some aspects of stimulus classification, reflecting primary processes of attentional allocation, memory and perceptual learning

(15). Moreover, it is also related to inhibitory processes and protection against interference from irrelevant stimuli (16-18). Attias et al. (14) showed reduced P2 amplitudes in tinnitus patients. The N2 component, occurring approximately 200ms post-stimulus, has been linked to early memory activation during selective attention and decision tasks (19). In a later study by Attias et al. (20), a prolonged N2 has been found in tinnitus patients. The P3 component, occurring approximately 300ms post-stimulus, is considered to reflect attention and a working memory update of change (21). Previous research showed changes in P3 in tinnitus patients, in which mainly an increased latency was found without changes in amplitude (1). In brief, ERP components N1, P2, N2 and P3 may be distorted in tinnitus patients, but consensus on which processes are disturbed by the tinnitus is currently lacking.

In addition, it is unclear whether ERPs can also objectify changes in auditory processing. Previous studies showed changes in ERPs after effective treatments in schizophrenia, dementia, depression, post-traumatic stress disorder and sleep apnea (22-27). Umbricht et al. (24) found a significant shortening of P2 and P3 latencies after risperidone treatment, suggesting an enhancement of the processing speed for allocation of attentional resources and updating of immediate memory. Furthermore, the shortening of N2 and P3 after continuous positive airway pressure treatment, found by Rumbach et al. (25), could be explained by changes in neurotransmitter metabolism. The treatment of dementia with cholinesterase inhibitors also resulted in a significant shortening of P3 (26). Finally, effects on the P3 amplitude were also described in literature. Surprisingly, two studies showed a decrease in amplitude (22,27), whereas one study showed an increase in amplitude (23). Hence, the interpretation of an amplitude change in ERPs remains unclear. Moreover, these ERP changes were correlated with the clinical improvement in the studies of Blackwood et al. (22) and Werber et al. (26), concerning treatments for schizophrenia and dementia. These findings suggest a potential role for ERPs to represent auditory processing changes. Yang et al. (28) showed an increase in N1 amplitude after repetitive transcranial magnetic stimulation in tinnitus patients. However, to date, published data on the change in ERPs after tinnitus treatments are scarce and the question arises whether ERPs may also provide insights into auditory processing of tinnitus patients and therapy effects after effective treatment.

Currently, self-report questionnaires are mostly used for the evaluation of tinnitus treatments due to the subjective nature of the tinnitus. The main disadvantage of this method is that it depends solely on the patients' responses. In particular, asking questions to patients may be susceptible to bias. Moreover, the majority of the tinnitus questionnaires exceeds the reading level recommended by health literacy experts (29). There is still no consensus on which questionnaire properly reflects tinnitus severity, possibly due to the heterogeneity within the tinnitus population (30). A final limitation is the considerable influence of the psychiatric state on the patients' perception and reaction, considering the complex interplay between depression symptoms and chronic tinnitus (31-34).

A tinnitus treatment which aims to change the brain activity in tinnitus is high-definition transcranial direct current stimulation (HD-tDCS). HD-tDCS induces cortical plasticity and modulates the activity of the brain structures. In our recent study, we found a significant improvement in TFI total score and a significant clinical improvement in 31% of the tinnitus patients after HD-tDCS (35). This study confirmed the positive effects of HD-tDCS on tinnitus perception previously found by Shekhawat et al. (36). Moreover, Shekhawat and Vanneste (37) confirmed the significant reduction in tinnitus loudness due to HD-tDCS by adding a sham group to their study.

The objective of the current study was to explore whether ERPs change after HD-tDCS treatment. The results add an important contribution to tinnitus research, since there is need for objective measurements to evaluate the effects of therapeutic interventions.

Methods

Subjects

A total of 22 chronic (>6months), non-pulsatile tinnitus patients were included. Patients who had a middle ear pathology or had ongoing tinnitus treatment were excluded. Demographic details are summarised in table1.

Study design

Figure 1 illustrates the study design. ERP recordings and questionnaire assessments were conducted at pre-therapy and follow-up (±six weeks after last treatment session). At post-therapy, the questionnaires were filled out, without ERP recordings.

Questionnaires

The patients completed the Tinnitus Functional Index (TFI) (38,39). This self-report questionnaire measures the negative impact and severity of tinnitus. The subject must answer each of the 25 questions on a 10-point Likert scale. A 13-point reduction is considered clinically significant (38,39).

Screening for anxiety and depression was performed with the Hospital Anxiety and Depression Scale (HADS). This 14-item self-report scale uses four answer possibilities and consists of two subscales: depression and anxiety. A cut-off score of eight points in each sub-scale is used for signs of either depression and/or anxiety (40).

ERP recording

Patients were tested with an auditory oddball paradigm in which frequent 1kHz pure tones (80% probability) and infrequent 2kHz pure tones (20% probability) were presented through shielded headphones (ATH-M30X). The rise and fall time of the stimuli were both 5ms. Patients were seated in a comfortable chair in a light-attenuated room and were instructed to push a button on a remote control each time they heard the target stimulus. During this task, EEG was recorded (Micromed-TM-SD-LTM-64-Express). An elastic cap was used to record from 31 Ag/AgCl electrodes, which were referenced to an electrode located at the chin. The ground electrode was placed on the right mastoid. The impedance measure for each electrode was at least below 5kΩ. Vertical electrooculogram was recorded using one electrode located below the right eye. The EEG was sampled at 1024Hz with 22-bit A/D resolution and band passed between 0.02Hz-450Hz. The stimuli were delivered with Presentation-TM (Neurobehavioral Systems, Inc).

ERP analysis

All data were analysed by the same researcher using Gilat-Medical-TM analysis software. Recordings were first segmented into time epochs that were time locked to the stimuli. Baseline correction for each trial was performed. All trials were averaged according to the condition (target and non-target), followed by a correction for external artefacts (e.g. eye blinks) by use of Independent Component Analysis (ICA) algorithm.

In a second step, the peak latency and peak amplitude were identified using analysis software which selected the maximum amplitude within specific time windows on the average for the target condition. Furthermore, the reaction time was defined as the time from stimulus onset to the button press.

In a final analysis, a group average for the target and non-target records of the pre-therapy and the follow-up visit was performed.

HD-tDCS

All patients received a total of eight sessions of HD-tDCS with two sessions weekly. In each session, a constant direct current of 2mA was applied at the right dorsolateral prefrontal cortex (DLPFC) for 20 minutes (figure2).

Statistical analysis

The objectives of the current study were (1) the evaluation of the potential of ERPs as an objective measure of auditory processing changes after HD-tDCS and (2) to determine whether these changes were correlated with the change in TFI.

The results concerning the questionnaires at the post-therapy visit are shown in the results section. However, the research questions evaluate the change from the pre-therapy to the follow-up visit, because the post-therapy visit was expected to be too soon to show therapy-related changes (35). Hence, a change in outcome measure was determined by calculating the difference between the pre-therapy and the follow-up visit.

The Shapiro-Wilk test was performed to evaluate the normality of the dataset. In addition, the normality was determined by visualising the data in histograms. The normality of the data was confirmed.

The effect of the HD-tDCS treatment on the TFI was tested using linear mixed models. Concerning the first research question, the Pearson correlations between the ERP parameters and the TFI total score at the pre-therapy visit were determined. In addition, we performed a paired samples t-test comparing the ERP parameters between the pre-therapy and the follow-up visit. The second research question was evaluated by a Pearson correlation test. Moreover, the ERP changes were compared between responders (i.e. TFI change ≥ 13) and non-responders (i.e. TFI change < 13) using independent samples t-tests. The significance level was set at $p \leq .05$.

Ethics committee approval

The Committee for Medical Ethics of the University Hospital Antwerp approved the study (file number: 16/41/415). All participants gave written informed consent.

Results

Effect of HD-tDCS on tinnitus questionnaires

The analysis of the therapy effect over time for HD-tDCS of the right DLPFC showed a significant improvement in TFI total score (p=.05) (figure3). A post-hoc comparison between the three visits revealed a significant difference between the pre-therapy and the follow-up visit (p=.04) and the post-therapy and the follow-up visit (p=.05). Moreover, 36% of the patients showed a clinically significant improvement (i.e. decrease of 13 points on the total score).

HADS indicated elevated signs of depression in 59% of the patients at pre-therapy visit. At follow-up visit, there were still 36% of the patients showing these signs.

Effects of HD-tDCS on ERPs

Prior to evaluating the change in ERP parameters, the correlations between these parameters and the initial TFI total score were evaluated, but there was no relationship present in the data (p>.05).

The comparison of ERP parameters before and after HD-tDCS was performed for all 31 electrodes (after exclusion of the eye bottom electrode). For all electrodes, there was a significant shortening of the N1 and P2 latency. The N2 latency was also significantly shorter, except for the most frontal electrodes FpZ and Fp2. The change in P3 latency depended strongly on the electrodes' locations. There was no significant change for the frontal, fronto-parietal, temporal and central brain electrodes, while the shortening was significant for the parietal, central-parietal, fronto-central, temporo-parietal and occipital electrodes. On the other hand, the N2 amplitude increased significantly, except for one of the most frontal electrodes Fp1. The P1 latency and the amplitude of the P1, N1, P2 and P3 components did not change significantly after HD-tDCS. No significant differences in reaction time parameters (i.e. the reaction times and correctness) were found prior versus follow-up HD-tDCS.

To keep an overview of the main ERP changes, the most central electrode Cz was focused since it shows the most prominent ERP components (table 2a-b). Figure 4a illustrates the average peak latency and amplitude prior to treatment and at six weeks follow-up. The percentage of patients showing N1, P2, N2 and P3 shortening on Cz was 86%, 68%, 68% and 64% respectively. The N2 amplitude of Cz increased in 73% of the patients.

Correlations between ERP findings and TFI changes

Prior to investigating the correlations between the ERP changes and TFI changes, the initial ERP parameters of the responders (i.e. TFI change≥13) and non-responders (i.e. TFI change<13) were evaluated. While there was a trend for the latencies being longer (except for P3) and the amplitudes being shorter (except for P2) in the responder group, this observation was only significant for the latency of P2 (p=.030). The mean P2 latency was 185ms in the non-responder group and 220ms in the responder group.

The question arose if the changes in TFI were correlated with the change in ERPs. As shown in table 2c, there were no significant correlations between the change in TFI total score and the change in ERP latencies and amplitudes at Cz, except for the correlation with the P1 latency change (figure4b). After removing the outlier with the highest change in TFI, this correlation was still significant (r=.50; p=.020). This latter correlation was positive, meaning that as the TFI total score decreases, the P1 latency also decreases and vice-versa. Moreover, the change in P1 latency was significant after correcting for the change in TFI total score (p = .020). Changes in ERPs were also compared between responders and non-responders. The results were in agreement with the correlation analysis, as the P1 latency change differed significantly between the two groups (p=.045) and the change in the other ERP parameters did not differ significantly between the two groups.

Discussion

The P1 component did not change significantly after HD-tDCS, indicating no change in this early auditory process of sensory gating. This finding is in line with previous research by Dornhoffer et al. (9), which showed no deficit for this process in tinnitus patients. Consequently, it is less likely that earlier AEPs will change either after tinnitus treatment, as distortions in these earlier responses in tinnitus patients were not previously found (1).

The current study showed significant shortening of the N1 component, which may reflect faster attentional and working memory operations. Since previous studies showed an increased N1 latency in tinnitus patients (1), this change after HD-tDCS may reflect better timing of the auditory processing. Conversely, the N1 amplitude did not change significantly, though it is reduced in tinnitus patients (14). In brief, these operations took less time after HD-tDCS without an increase in synchronized neuronal activity.

The P2 component occurred significantly earlier after HD-tDCS, which may indicate faster inhibitory processes for irrelevant stimuli, though there was no significant change in P2 amplitude. This is in contrast with current literature, where Attias et al. (14) showed a reduced P2 amplitude in tinnitus patients and no studies indicate differences in P2 latency between tinnitus and non-tinnitus subjects.

The significant shortening of the N2 component in the current study may be associated with faster, early memory activation. As literature showed that the N2 latency was increased in tinnitus patients (20), this change may reflect a more adequate timing of these auditory processes after HD-tDCS. Moreover, the N2 amplitude increased significantly, indicating that the synchronized neuronal activity became more efficient. However, the shortening of the N2 latency was not significant for FpZ and Fp2 and the N2 amplitude did not increase significantly for Fp1, possibly due to the eye blink correction procedure.

The earlier appearance of the P3 component in the current study may reflect faster working memory updates of change. Previous studies demonstrated an increased P3 latency in tinnitus patients (1) and the change in P3 latency, found in the current study, may indicate that the auditory processing became more comparable to those of non-tinnitus subjects.

In summary, P1 was unchanged after HD-tDCS, which is in line with literature showing no distortion in the P1 component in tinnitus patients. Moreover, subsequent components changed in latency, but only N2 changed in amplitude. In other words, the timing of the sound processing was faster after HD-tDCS, but there was no change in the extent to which neural resources were allocated to these processes, except for early memory activation component N2. However, the interpretation of these results is limited, as there was no relationship between the ERP values and the TFI total scores at the pre-therapy visit. Moreover, it was not possible to state if the ERPs of the participants were abnormal due to the absence of a matched-control group.

In order to provide a better understanding of this change in ERPs, the initial ERP parameters of the responders and non-responders were evaluated. This showed a trend of longer ERP latencies and shorter ERP amplitudes for the responders. It might be that patients whose ERPs are distorted are more likely to benefit from HD-tDCS, but further research is needed to interpret ERP parameters in tinnitus research. Contrary to expectations, there was no correlation between the change of this parameter and the change in TFI. Also the correlations between the other ERP parameters and the change in TFI were not significant, except for the positive relationship between the shortening of P1 and improvement in TFI total score. It may be that the P1 latency is responsive to change in TFI. However, these data must be interpreted with caution because of multiple testing. Nevertheless, this finding does not contribute to the understanding of significant ERP changes, which is in line with the literature on ERPs in other research areas, as they did not find either a consistent correlation between the objective measure and subjective reporting. Exploring influencing factors in the current study is limited due to the small therapeutic effect and number of participants.

The discrepancy between the percentage of patients showing a change in ERPs and the percentage of patients showing a change in tinnitus perception could be attributed to individual factors. The mental status of a subject, for instance, may influence the scores on tinnitus questionnaires (34). Patients who are depressed or lack effective coping mechanisms may excessively focus on their tinnitus to benefit from HD-tDCS. Four patients who showed elevated signs of depression on the HADS did not improve on the TFI total score, while their ERPs showed a more efficient sound processing. Hence, future studies should aim for the inclusion of a more homogeneous group of tinnitus patients.

Importantly, the reaction time parameters did not change after HD-tDCS in this study, suggesting that the reported changes in ERPs were not caused by task learning. An important objective for future studies will be to investigate ERP changes after other tinnitus treatments to clarify if the ERP change is due to the treatment itself. However, treatment options for tinnitus are not compliant with a one-size-fits-all approach, hampering the development of ERPs as an objective marker of tinnitus experience, thus the addition of self-report (i.e. subjective) assessments is inevitable.

As this pioneering study explored the relevance of ERPs in the assessment of therapeutic effects in tinnitus patients, it has shed light on the needs for future studies. Firstly, there is a need for normative data, by adding a control and/or sham group, in order to understand fully the change in ERPs. Secondly, a contribution may be added by replicating this study with other tinnitus treatments. Finally, future studies should include a larger and more homogenous group of participants.

To conclude, the current study shows that that adding ERPs to the outcome measures in tinnitus research may lead to a better understanding of the therapeutic effects. Results showed a shortening of

ERP latencies and an increased N2 amplitude, possibly reflecting more effective sound processing with higher recruitment of synchronized neurons in the auditory cortex. Yet, these changes are not correlated with the subjective tinnitus perception. Although the oddball task was conducted twice, the reaction times did not change. Hence, the changes in auditory processing are not due to a learning effect. Future studies should elaborate on these results to provide a better insight in the underlying mechanism of the ERP changes after tinnitus treatment.

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Figure legends

Figure1: Patient flow diagram of the study: each patient receiving eight sessions of HD-tDCS. Tinnitus perception is assessed at three visits: pre-therapy, post-therapy and follow-up (HD-tDCS, high definition tDCS; , event-related potentials; , tinnitus questionnaires).

Figure2: The HD-electrodes were positioned at the right DLPFC according to the 10/20 international system for EEG electrode placement, with the central anode at F4 and the adjoining cathodes at F2, F6, FC4 and AF4. This direct current was transmitted by means of five sintered silver/silver chloride (Ag/AgCl) ring electrodes with an outer radius of 12mm and an inner radius of 6mm and delivered by a battery-driven 1x1 tDCS low-intensity stimulator and 4x1 multichannel stimulation adaptor (Soterix Medical Inc, New York), with a maximum output of 2mA and a fade-in and fade-out of 20 seconds (left). The current flow with HD-tDCS at the right DLPFC is simulated with Soterix HD-Explor TM 4 (right). © Soterix Medical Inc. (DLPFC, dorsolateral prefrontal cortex).

Figure3: The evolution of the TFI total score over time at pre therapy (before the first tDCS session), post therapy (after the last tDCS session) and follow-up (± 6 weeks after the last tDCS session) for each individual (n=22). The black solid line represents the mean TFI total score. Significant changes (p<.05) over time are indicated with an asterisk (*). (TFI, tinnitus functional index)

Figure4: AEPs of Cz electrode prior and follow-up HD-tDCS. The latency and amplitude values are reported in table2 (A). The scatterplot between the change in P1 latency of Cz and the change in TFI total score (B). (TFI, tinnitus functional index)