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The Effect of an Aversive State on Brainstem Auditory Evoked Potentials (BAEP) in Humans

An EEG study investigating the influence of an induced aversive state on the BAEP in Healthy Controls

Master thesis Neuropsychology

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Background: *The defence network is a network of brain structures that are activated when a person experiences fear or anxiety. Structures in this network, such as the amygdala, locus coeruleus (LC) and the inferior colliculus (IC), show heightened activation in aversive states. It is known that the IC generates Wave V of Brainstem Auditory Evoked Potentials (BAEP). BAEP are auditory reflexes which serve to localize oral stimuli. If a situation is experienced as potential threat, these reflexes might be heightened to initiate a faster response. The study of Baas, Milstein, Donlevy and Grillon (2006) investigated this hypothesis by testing how BAEP respond to an experimentally induced aversive state in healhy controls. They indeed found heightened amplitudes of Wave V. This study will serve as replication of the study of Baas et al. (2006).*

Method: *BAEP was measured during a threat and safe condition in a sample of 13 healthy participants. Auditory stimuli activated Wave V. The aversive state was induced by an threat-of-shock paradigm. A paired samples t-test compared the peak-to-trough difference of Wave V in both conditions. A bivariate Pearson correlation investigated the possible relationship between trait anxiety, measured using the Spielberger State-Trait Anxiety Inventory (STAI), and the amplitude of Wave V.*

Results: *The results showed no significant difference in the amplitude of Wave V under threat of shock. There was no correlation between trait anxiety and the amplitude of Wave V.*

Conclusion: *The assumption that Wave V is modulated by an aversive state, could not be supported.*

Key-words: brainstem auditory evoked potentials; Wave V amplitude; induced state of anxiety; defence network; spielberger state-trait anxiety inventory

Fear and anxiety are closely related aversive emotional phenomena centered around threat. They both involve intense negative feelings and bodily manifestations (Öhman, 2008). Over the past few years, research has started to unravel important differences between them. Fear is a deeply wired reaction in the brain to certain situations or objects, which may or may not represent real danger. It allows organisms to biologically adapt to harmful circumstances. Therefore, fear has always been vital in survival (James, 1890; Mowrer, 1939; Öhman, 2008). Anxiety on the other hand, reflects a more diffuse, unpleasant, vague sense of apprehension often in response to an imprecise or unknown threat (James, 1890; Mowrer, 1939; Öhman, 2008). In addition, it is a less instinctive reaction compared to fear (Sadock, Sadock & Ruiz, 2015). Therefore, fear is triggered by an identifiable threatening stimulus whereas anxiety is based on the anticipation of possible threatening stimuli (Öhman, 2008).

In the late 19th century, experimental brain research was initiated and quickly started to predominate the field of neuroscience. As a result, neuroscientific research revealed some biological underpinnings of fear and anxiety (LeDoux, 2012). This led to the discovery of the defence network (Davis & Whalen, 2001), a network of brain structures that are activated when a person experiences fear and/or anxiety. There are many structures involved in this network, the most important being the amygdala and the locus coeruleus (LC, Baas et al., 2006; Wilde, 2009). Human imaging studies uncovered the amygdala as the central structure of this network (Davis & Whalen, 2001). The amygdala is known to be responsible for all kinds of emotions. Beyond its role in emotional reactivity, animal studies also revealed its importance in emotional learning. Cues can gain significance through association with rewarding or aversive events (Gallagher & Chiba, 1996). Therefore, the amygdala has a crucial role in the fear response. Further research showed that not only the amygdala, but also the LC is of great importance. This structure receives its input from the amygdala and initiates basic fear responses, such as an increased heart rate, pupil dilation, increased blood pressure and sweating (Wilde, 2009). The LC releases the neurotransmitter norepinephrine in response to pain and stress, which activates the sympathetic nervous system and causes the adrenal glands to produce the stress hormone cortisol (Wilde, 2009). This initiates the fight or flight response, a physiological reaction that occurs in response to a perceived threat. Several studies suggest that the LC is the main generator of this response (Baas et al., 2006; Wilde, 2009).

Another brain structure possibly involved in the defence network is the inferior colliculus (IC). Some studies have implicated the IC is involved in defensive behaviour, or even

claimed it belongs to the main structures of the defence network (Brandao et al., 1993; Graeff, 1990; Maisonnette et al., 1996). Evidence for these claims is mainly derived from animal studies. One of these studies showed that stimulation of the central nucleus of the IC leads to defensive behaviour, like alertness and the fight or flight reaction (Maisonnette et al., 1996). Research reveals the IC as a major synaptic station in the auditory midbrain (Gutfreund & Knudsen, 2006; Mansour, Altaher & Kulesza, 2019; Olsen, Knudsen & Esterly, 1989; Wise & Irvine, 1985). The central nucleus of the IC provides frequency-specific information about the localization of sounds and sends this information to the external nucleus of the IC. The external nucleus integrates, recognizes and discriminates the incoming information and forms a so-called auditory space map (Gutfreund & Knudsen, 2006; Olsen et al., 1989; Wise & Irvine, 1985). Over the past few years, research focused on measuring the IC activity by using neuroimaging methods (Moerel et al., 2017). Besides using fMRI, researchers discovered that the IC could also be measured by using brainstem auditory evoked potentials (BAEP) (Baas et al., 2006; Drake, Pakalnis, Phillips, Padamadan & Hietter, 1991; Jewett & Williston, 1971; Knott, Stelmack, Mileto & Beauchamp, 2003). BAEP are auditory reflexes, which serves to localize oral stimuli, recorded from the surface of the scalp during brief auditory stimulations. These reflexes might be heightened to initiate a faster response in case of an potential threat. BAEP consist of five waves, labelled I to V which can be measured by electroencephalography (EEG) (Baas et al., 2006; Moerel et al., 2017). Literature suggests that the IC is the main generator of Wave V in BAEP (Baas et al., 2006; Graeff. 1990; Laumen, Ferber, Klump & Tollin, 2016), which could therefore be affected during threat.

Previous studies showed deviations in Wave V in people diagnosed with several psychological diseases. For example, people diagnosed with anxiety disorders, obsessive-compulsive disorders and even borderline personality disorders, showed a higher amplitude of Wave V compared to healthy controls (Drake et al., 1991; Drake, Phillips & Pakalnis, 1991; Nolfe, Serra, Palma & Buscaino, 1998). However, there is not much research on whether Wave V is affected by an induced state of anxiety in healthy volunteers without a history of psychological diseases. Therefore, the study of Baas et al. (2006) tried to shed some light on this matter. Baas et al. (2006) investigated whether there is heightened activation in structures involved in defensive states by testing BAEP during experimentally induced anxiety in healthy volunteers. They hypothesized that anticipation of shock affects the latency and amplitude of the BAEP Wave V due to the activation of the defence network. The study found that shock anticipation by an induced state of anxiety indeed increased the amplitude of Wave V in healthy

controls, as it was also observed in anxiety disorders. This suggests that fear in general affects the processing of sensory information at a very basic level, which makes it insensitive to cognitive manipulation (Baas et al., 2006). The current study is a replication of the study of Baas et al. (2006), and aims to validate the findings of this prior research and to contribute to generalizability of the results. In addition, the current study also investigated if there is a relationship between the level of anxiety experienced in daily life and the amplitude of Wave V in BAEP.

Method and materials

Participants. Twenty-five subjects participated in this study. Five participants were tested in the pilot phase to determine which frequency (Hz) resulted in the most defined brain waves and twenty participated in the final experiment. Four participants (N=4) had to be removed from the analysis because they were accidently enrolled in a different version of the experiment exposing them to a frequency of 36 Hz instead of 18 Hz. Before the statistical analysis was done one participant had to be excluded due to a hardware error (N=1) and one (N=1) dropped out during the experiment. One outlier was detected and removed (N=1). Hence, the final sample consisted of 13 participants (N, Mean Age = 23.4 years, SD = 2.4).

In order to be included in the study, the participants had to be between 18 and 60 years old, with no history of epileptic attacks, and no use of psychiatric medication. Participants were recruited by handing out flyers and advertising on social media. The study took place in the science laboratory at Utrecht University. Informed consent was obtained from all participants. This research was approved by the Faculty Ethical Review Committee (FETC).

Stimuli and apparatus. In this experiment Biosemi was used to measure the incoming signals from five AgCl flattype electrodes. Three of those were Auditory Brainstem Response (ABR) electrodes. The ABR cord had 3 active electrodes behind the left ear, behind the right ear and one on the forehead as reference. The other two AgCl flattype electrodes, Common Mode Sense (CMS) active electrode and Driven Right Leg (DRL) passive electrode, were used to ground the system. These electrodes were placed left and right from the ABR electrode on the forehead. All electrodes were attached with adhesive disks and Signa gel. The auditory responses (clicks) were collected and verified by using Chronos. Chronos is a device which collect responses and presents stimuli (sounds). It can detect the precise source of sounds as well as its timing and provides consistent latency output across devices (NITRC, 2017). The auditory clicks were administered binaurally through headphones. The click duration was 100 microseconds with a frequency of 18 Hz. The Digitimer DS7A was used to administer the shock

stimuli through a bracelet on the non-dominant wrist. Five shocks were administered during the shock work-up and two during the experiment. The duration of the shocks was in total 750 milliseconds (ms) per shock (150 times 2ms shock with a 3ms break). The intensity of the shocks ranged between .5 and 2.5 mA

Procedure. Before the experiment began, the participants filled out the Spielberger State-Trait Anxiety Inventory (STAI) to determine their level of anxiety experienced in daily life. This self-report questionnaire measures the severity of symptoms of anxiety and the general tendency of feeling anxious (Julian, 2011; Kayikcioglu, Bilgin, Seymenoglu & Deveci, 2017). The STAI consist of two anxiety concepts, namely state anxiety and trait anxiety. For this study, only the part which measured trait anxiety was used to investigate the amount of anxiety participants experienced in daily life. The range of possible scores for both state and trait anxiety varies from 20 to 80. The scores are classified as "no or low anxiety" (20-37), "moderate anxiety" (38-44) and "high anxiety" (45-80) (Kayikcioglu, Bilgin, Seymenoglu & Deveci, 2017). Participants also underwent a shock work-up prior to the experiment to determine the individual tolerance. They received a total of five shocks of which they had to rate the intensity on a 5-point scale: 1 = not all all, 2 = slightly, 3 = moderately, 4 = quite a bit, 5 = extremely. The intensity of the next shock was based on the rating of the previous shock. The goal of this work-up was to adjust the shock intensity to the personal experience of the subject, selecting only the shocks rated at least 4-points.

The experiment consisted of two runs, 9 minutes each, with 8 safe and 10 threat blocks. The two threat blocks in which the shocks were administered, were excluded from analysis. The experiment was not randomized, as the safe and threat blocks alternated. The threat conditions were signaled by the appearance of a red triangle on the screen in combination with instruction text which stated: "Shock only during red square". The safe condition was indicated by a blank screen with a black fixation cross and the same instructions. The duration of each block was approximately 34 seconds. Binaural clicks were administered in both conditions, in total 9792 clicks in the safe condition and 9792 in the threat condition. The first shock was administered at the end of the first run during the eighth occurrence of the red triangle. The second shock was administered at the beginning of the second run during the first occurrence of the red triangle.

At the end of the experiment, participants had to complete a subjective rating to assess their overall fearfulness, calmness, energy, and drowsiness during the both conditions. These ratings were also based on a 5-point scale: 1 = not all all, 2 = slightly, 3 = moderately, 4 = quite a bit, 5 = extremely.

Data measurement and analysis. One outlier (N=1) was detected and removed from the dataset because the peak-to-trough difference in the safe and threat condition was far outside the expected range (the amplitude almost doubled). The ABR was processed and transferred to Brainvision Analyser for further analysis. The results were filtered between 30 and 3000 Hz because results out of this range would likely provide unsusceptible data. In addition, amplitudes of 200 μV/ms or higher were also removed from the dataset during the raw data inspection. Furthermore, the peaks and troughs of Wave V were marked in Brainvision Analyzer and exported to SPSS. The difference between peak and trough was tested for significance using a paired-samples t-test. In addition, the correlation between the difference in peak and trough of Wave V and the STAI was conducted by using a Pearson Correlation.

Results

In order to evaluate the effectiveness of the threat-of-shock paradigm, participants had to complete a subjective rating to assess their overall fearfulness, calmness, energy, and drowsiness during the both conditions. The results from the paired-samples t-test t (12) = 7.89 p >.001, showed significantly higher reported anxiety in the threat (M = 2.23, SD = .73) compared to the safe condition (M = 1.15, SD = .38).

Wave V amplitude

To test if the difference between peak and trough of Wave V in the threat condition is higher compared to the safe condition, a paired-samples t-test was performed in SPSS. Prior to conducting the analysis, the assumption of normality was examined by using the skewness and kurtosis levels. In the safe condition, the skewness was .23 and it was .17 in the threat condition. The distribution is considered approximately symmetric if the skewness levels are between -.5 and .5, which applies in both conditions (Field, 2017; George & Mallery, 2010; Gravetter & Wallnau, 2014; Trochim & Donnelly, 2006). The kurtosis was -1.11 in the safe condition and in the threat condition -1.3. Kurtosis values need to be between the -2 and 2 in order to be considered approximately symmetric (Field, 2017; George & Mallery, 2010; Gravetter & Wallnau, 2014; Trochim & Donnelly, 2006). Therefore, the kurtosis falls between the acceptable limits. Unfortunately, these statistics are unstable in small samples, so their results should be interpreted with caution (Field, 2017). Figure 1 displays the group mean waveforms of the total sample of participants in the threat as well as the safe condition. This figure shows an overall higher difference between peak and trough in the threat condition compared to the safe condition for all waveforms. However, the results from the paired-samples t-test t (13) =

.253, p = .805, show no significant difference in the amplitude of Wave V between the safe (M = .33, SD = .16) and threat condition (M = .32, SD = .15).

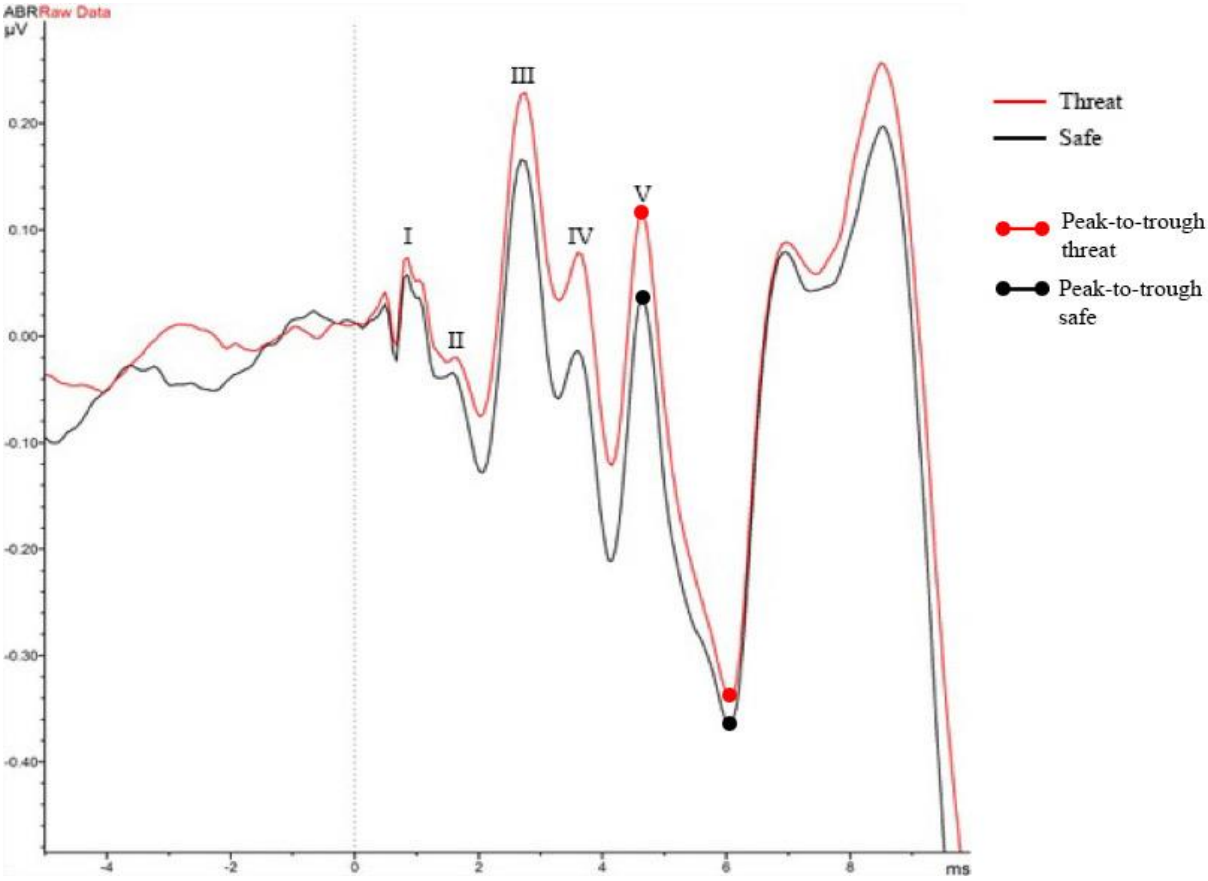

Figure 1. Mean sample waveforms I-V (click frequency 18 Hz).

Relation between trait anxiety and Wave V amplitude

To test if there is a correlation between the STAI scores and the difference between peak and trough of Wave V in the threat condition, a bivariate Pearson correlation was conducted in SPSS. The results showed no significant correlation (r = .12, p = .70) between the STAI scores (M = 36.69, SD = 9.13) and the amplitude of Wave V in the threat condition (M = .32, SD = .15). In addition, the results also showed no significant correlation (r = .18, p = .56) between the STAI scores and the amplitude of Wave V in the safe condition (M = .33, SD = .16).

Discussion

It is generally assumed that the IC is part of the human neural defence network and the main generator of Wave V in BAEP (Baas et al., 2006; Brandao et al., 1993; Graeff, 1990; Laumen et al., 2016; Maisonnette et al., 1996). Therefore the IC might play a role in threat processing. Based on these assumptions, the current study hypothesized that an aversive state

in humans could affect Wave V in BAEP. It is a replication of the study of Baas et al. (2006), and aims to validate the findings of this prior research and to contribute to generalizability of the results. In addition, this study also investigated if participants who are generally more anxious will have a higher amplitude of Wave V in BAEP.

This study, examining the effect of an experimentally induced state of anxiety on the amplitude of Wave V in BAEP, did not indicate a relationship between anxiety and the amplitude of Wave V. Although threatening participants with shocks elicited a sustained state of anxiety, this result did not reflect in the Wave V in BAEP. Therefore, the assumption that Wave V is modulated by an aversive state, could not be supported in this study and additional research is needed to investigate this further.

Building on previous research (Baas et al., 2006), the correlation between general level of anxiety and the amplitude of Wave V in the threat condition was examined. The results showed no relationship between the level of trait anxiety and Wave V in the threat condition, and upon further investigation, neither in the safe condition. Furthermore, the earlier suggested theory that aversive states affect information processing at a very basic level, leaving it unaffected by cognitive manipulation, cannot be confirmed by these outcomes. All results combined, this study did not replicate the findings of Baas et al. (2006).

This study had several limitations. First of all, as mentioned not all data could be used for analysis which reduced the sample to 13 participants. This can be considered a small sample size as previous studies in this area consisted of at least 15 participants. Therefore, future research should include more participants to increase the likelihood of finding a significant effect. In addition, at least 30 participants are needed in order to find a solid correlation (Field, 2017). Second, the STAI was used to determine the level of anxiety. Since this is a self-report questionnaire, it is possible the results contain a self-report bias which might cause validity problems. This self-report bias should be taken into account when interpreting the results. Third, this study included participants based on a few criteria. Participants had to be between 18 and 60 years old, with no history of epileptic attacks, and no use of psychiatric medication. However, hearing impairment was not one of the exclusion criteria. Studies showed that hearing loss can influence the BAEP outcomes (Attias, Urbach, Gold & Shemesh, 1993; Esteves, Dell Aringa, Arruda, Dell Aringa & Nardi, 2009). Future studies on this topic should use hearing impairment as an exclusive criteria. Finally, although the reported level of anxiety was significantly higher in the threat condition compared to the safe condition, an average of 2.23 on a 5-point scale reflects only ‘slightly anxious’. Whereas the study of Baas et al. (2006) reported an average anxiety level of 3.3 in the first and 3.0 in the second experiment. A possible

explanation for this difference is the experimenter demands effect. This effect refers to the unconsciously change in behavior of the participants in response to the attitude of the experimenter (Zizzo, 2010). For example, because the use of electric shocks initially scared most participants from applying for the study, attenuating the shock effects was sometimes needed to convince them to participate. It might be possible that easing the participants beforehand let to a lower reported level of anxiety. This might explain the differences between the findings of the current study and the study of Baas et al. (2006).

Although these limitations must be considered in future research, this study still has important implications for theory and practice. The current study contributes to developing more theoretical knowledge concerning the effect of anxiety on the auditory processing in the IC of healthy controls. It questions if Wave V can be modulated by an aversive state. As it has been more established if threat indeed effects Wave V in people with anxiety disorder (Drake, Pakalnis, Phillips, Padamadan & Hietter, 1991), future research could focus on examining significant differences in the results of people diagnosed with anxiety disorders and those of healthy controls within the same study. If future research establishes that threatening situations affects healthy people differently than people with an anxiety disorder, this could also have practical implications on the treatment of these disorders. It might result in treatment programs taking this difference into account and controlling/limiting sensory stimuli as much as possible in the diagnostic practice.

Conclusion

This study investigated the influence of an induced aversive state on Wave V in BAEP in healthy participants. The results indicated no relationship between anxiety and Wave V in BAEP. Although earlier research suggests a relationship between anxiety disorders and Wave V (Drake, Pakalnis, Phillips, Padamadan & Hietter, 1991; Drake, Phillips & Pakalnis, 1991; Nolfe, Serra, Palma & Buscaino, 1998), this study did not show this relationship in healthy participants. As a result, this study contradicts the outcomes of the study of Baas et al. (2006), which did find that the brainstem response in healthy controls resembles that of people with anxiety disorders. Moreover, no relationship between the level of trait anxiety and Wave V in the threat condition. Inducing a state of anxiety did not seem to affect healthy participants differently, regardless of their self-reported level of anxiety. All outcomes combined, the assumption that Wave V is modulated by an aversive state, could not be supported by this study. Despite some of the limitations, the results could contribute to the development of knowledge

in this field. Future research could deepen the understanding by increasing sample size, using stricter excluding criteria and comparing people with anxiety disorders to healthy controls.

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