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VILNIUS UNIVERSITY

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MĖLYNYTĖ

Sex differences in auditory-evoked electrical brain activity: a case of N2 and P3 waves

DOCTORAL DISSERTATION

Natural Sciences
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VILNIAUS UNIVERSITETAS

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MĖLYNYTĖ

Klausos stimulų sukelto elektrinio smegenų aktyvumo lytinių skirtumų įvertinimas - N2 ir P3 bangų tyrimas

DAKTARO DISERTACIJA

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ABBREVIATIONS

ABR – auditory brainstem responses

ACC – anterior cingular cortex

ANOVA – analysis of variance

EEG – electroencephalography

ERP – event-related potential

GFP – global field power

ICA – Independent Component analysis.

ISI – inter-stimulus interval

LP – late potential

LRP – lateralized readiness potential

MMN – mismatch negativity

MRI – magnetic resonance imaging

OAE – ottoacoustic emission

OCD – obsessive-compulsive disorder

PET – positron emission tomography

RM-ANOVA – repeated measures ANOVA

RT – reaction/response time

SE – standard errors of mean

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INTRODUCTION

Electroencephalography (EEG) is one of the techniques to evaluate the functioning of the human brain. It is a safe and non-invasive neuroimaging method when electrodes, placed on the scalp, enable to capture electrical activity arising from cortical neurons. Event-related potentials (ERPs) constitute a technique to measure averaged brain responses occurring to a repetition of a particular type of stimulus during a precise task. With the help of ERPs scientist can evaluate how quickly the brain processes a stimulus while performing a task and how strong the response is.

One of the widely investigated cognitive ERP components in scientific and clinical studies is an auditory P3. It is a great tool for evaluation of cognitive processes, therefore, along with other cognitive ERPs, it is of interest in neuropsychiatry (Kappenman & Luck, 2016; Sur & Sinha, 2009). Experimental tasks that are used to evoke ERPs vary and can capture different cognitive processes. For instance, an Oddball task is helpful in assessing the initiation and execution of response (that requires attention, working memory), whereas a Go-NoGo task – the inhibition of unwanted motor action (so called, executive functioning). Both functions are found to be impaired in psychiatric patients and that is reflected in ERPs. The auditory P3 is disturbed in people with schizophrenia and other psychosis, post-traumatic stress disorder, dissociative disorder, and it has been proposed as a potential electrophysiological biomarker (Luck et al., 2011).

Sex / gender[1] has an influence on the prevalence, age of manifestation onset and the severity of the symptoms of many psychiatric conditions (Bao & Swaab, 2010; Sánchez, Bourque, Morissette, & Di Paolo, 2010). However, sex effect on ERPs is often being neglected – some studies still exclude females from their samples or ignore sex as a factor in their findings (for review see Mendrek, 2015; Cahill, 2012), despite sex-specific morphology of auditory cortex and other brain areas related to cognitive abilities, such as attention, executive functioning (del Mauro et al., 2021; Good et al., 2001; Joel et al., 2015; Lotze et al., 2019; Ruigrok et al., 2014). Moreover, sex-

[1] A person could be attributed to be a male or a female by two aspects: the word "Gender" refers to person's inner awareness and self-attribution to a sexual identity, related to socially and culturally constructed roles, whereas "Sex" is defined as a biological sex established by functional, genetic specificity and related to the reproductive function and organ. This dissertation is concentrating on male/female as a biological variable and utilized the term "Sex", however studies that used any of the two terms, will be overviewed and looked at.

related auditory information processing and auditory scene perception should also be noted. For instance, the frequency, and the strength of cochlear response is greater in females and auditory responses at the brain stem are quicker in females than males (Boston et al., 1992; Krizman et al., 2019; Lotfi & Zamiri Abdollahi, 2012; McFadden, 1998; McFadden et al., 2021). On a behavioral level females tend to perceive auditory stimuli to be closer than it appears, they have better ability to filter out unrelated sounds (Lewald, 2004; Lewald & Hausmann, 2013; Neuhoff et al., 2009; Zündorf et al., 2011). It raises a question if the dissimilarities of basic auditory processing could reflect in cognitive brain responses, evoked with auditory stimuli.

Although the auditory P3 is a frequently investigated wave (e.g., search on PubMed database with entries for *auditory P300/P3* gives over 3700 articles), the effect of possible confounds including sex that could affect the auditory P3 is still debatable. To see the whole picture and draw conclusions on whether sex effect on the auditory P3 in simple auditory paradigms is important, a thorough overview and analysis of already published studies is needed. A systematic review or a meta-analysis would be the most suitable methods for this investigation. The systematic review uses precise, systematic methods to select, analyze and interpret the data with a non-bias approach. The knowledge would be of outmost importance for future clinical investigations, where P3-realted processes are of interest. It can also provide an insight into other factors that might contribute to the effect.

For a wide and efficient application of biomarkers for psychiatric disorders, it is important to consider tasks that are simple, quick, and non-tiresome. Barry and De Blasio (2007) have proposed a modified paradigm that is a midway between the auditory oddball task and the traditional Go-NoGo task (Barry et al., 2007; Barry & de Blasio, 2013). It is called an auditory equiprobably Go-NoGo paradigm. With the help of this paradigm the time of the experimental procedure is shortened, and the obtained neural responses share features of the two classical paradigms covering both initiation and execution of response and the inhibition of unwanted action. Along with the auditory P3 another cognitive ERP wave named N2 is normally assessed as it reflects cognitive control functioning. This paradigm could be a promising tool for the use in clinical settings, thus it is important to evaluate sex-related (dis)similarities in healthy population first. The results would provide understanding of the role of sex factor when setting a normative range of electrophysiological parameters that is important for neuropsychiatric application.

1.1. Aim and objectives

The aim of this thesis is to address sex-related differences in the electrical brain activity indexed by N2 and P3 components in response to auditory stimulation.

To achieve the aim the following objectives were formulated:

- To assess the effect of sex factor on amplitudes and latencies of N2 and P3 components from the auditory equiprobable Go-NoGo paradigm.
- To review and systemize the sex-effect related findings on the amplitudes and latencies of auditory P3.

1.2. Scientific novelty

In this thesis the following aspects were studied and performed for the first time:

- The effect of sex on ERPs in response to the equiprobable Go-NoGo paradigm in the sample where female group was balanced according to the menstrual cycle phase.
- The systematic review of sex effects on auditory P3.

1.3. Practical implication

- The understanding of possible effects of sex on N2 and P3 components from the equiprobable Go-NoGo paradigm will guide scientists in establishing the normative data for future application of the paradigm in clinical settings.
- The overview and systematic evaluation of sex-related effects on auditory P3 amplitude and latency will enable researchers and governmental health policy makers to create recommendations and allocate resources for consideration of sex-effects.
- Careful analysis of findings related to sex-effect on P3 parameters will help assessing the scale of the attention paid to the effect.
- The review will systematically gather all the related information (demographics, methodological data, other) that will assist in identifying other confounding factors.

1.4. Thesis statements

1. Based on the auditory equiprobable Go-NoGo task results:
   - Higher P3 amplitudes are observed in females; this is driven mainly by stronger P3 in Go condition, but no significant sex effect for P3 in NoGo is evident.
   - N2 amplitudes do not differ between sexes.
   - N2 and P3 latencies are longer in females than males.
2. A systematic review of sex-effect on auditory P3 revealed that:
   - P3 latencies are mainly comparable between sexes.
   - Sex effect on P3 amplitudes cannot be neglected: it is higher in females than males in half of the studies and indifferent between sexes in the other half.

OVERVIEW OF SEX FACTOR IN ELECTROPHYSIOLOGICAL STUDIES

2.1. Sex effect on auditory system

2.1.1. Brain structure

In the recent century neuroscientists started to pay more attention to whether sex related differences in the human brain are prominent and if so, at which regions those dissimilarities exist. Higher cognitive functions and interhemispheric transfer time is closely related to the morphology of the main fiber tract that connects the two hemispheres (Hinkley et al., 2012; Schulte et al., 2004). This fiber, called corpus callosum, has been found to be larger in females than males (Allen et al., 1991; Steinmetz et al., 1992). A study by Ingalhalikar et al. (2014) has shown sex differences of the human brain structural connectome (Ingalhalikar et al., 2014): female brains dominated in between-hemispheric connectivity, whereas males had a more pronounced within-hemispheric connectivity. The differences emerged at young age, the segregation is strongly observed at adolescent and adult subjects. Another large-scale study (that employed over 5000 participants) conducted by Ritchie et al (2018) also reported a structural and functional sex differences in the human brain. It found higher raw cortical thickness and white matter tract complexity as well as more pronounced connectivity in the default mode network in females, whereas males had higher raw surface areas and raw volumes and white matter tract fractional anisotropy (Ritchie et al., 2018). On average, distinct brain connectome in males and females could be attributed to different cognitive abilities, such as spatial processing and motor functions. For instance, sensorimotor speed is more efficient in males (as their intrahemispheric interaction), whereas females possess better functions needed for integration of both hemispheres, such as attention, word or face recognition and memory (Allen et al., 1991; Ingalhalikar et al., 2014; Steinmetz et al., 1992).

When structural brain differences were studied thicker grey matter was observed in temporal and parietal cortices in females independent of brain size (Sowell et al., 2007). Grey matter volume is found to be larger in females than males in regions of parietal, temporal, and frontal cortex (del Mauro et al., 2021; Luders et al., 2006; Lv et al., 2010). To name a few specific regions, larger volumes of inferior temporal gyrus (related to spatial abilities) are observed in males, whereas absolute grey matter volumes in right regions of inferior frontal gyrus, superior temporal area, more specifically, Heschl gyrus,

planum temporale, and superior parietal lobule – areas important in language and sound processing – are larger in females than males (del Mauro et al., 2021; Good et al., 2001; Joel et al., 2015; Lotze et al., 2019; Ruigrok et al., 2014). Also, anterior cingulate cortex (ACC) – an area related to impulse control and emotional correlates to actions, is larger in females than males (del Mauro et al., 2021; Lotze et al., 2019; Ruigrok et al., 2014).

It is worth mentioning, that it is still debatable if sex-specific brain patterns (so called "types") are present as these results represent averaged brain structures and functions, and a big variability of human brain structures and a considerate overlapping data between the sexes have been reported (Joel et al., 2018). Although, when exploring cognitive abilities not the actual structure but the function is the key – and "female brain" and "male brain" should be attributed to the function specific to a certain sex (Glezerman, 2016). Saying that, as this thesis is concentrating on averaged physiological measures that could lead to a normative measure, it is important to evaluate sex effect on the two groups rather than sex types of a function.

2.1.2. Auditory information processing

It is documented that females tend to have better auditory abilities and healthier hearing health than males (Lien & Yang, 2021). Auditory information is not always processed in the same manner when sex is concerned. Firstly, the functioning of outer hair cells of the cochlea that is assessed with otoacoustic emission (OAE) is weaker in males than females. Females produce more numerous and stronger spontaneous OAEs, and higher amplitudes to click-evoked OAEs as compared to males (Snihur & Hampson, 2011). Secondly, some components of auditory brainstem responses (ABR) – that reflect neural activity from cochlea to brain stem – differ in latencies and amplitudes between sexes. For example, females have shown larger amplitudes of I component (that is, a cochlea nerve response), shorter wave-I-V inter-peak intervals, shorter and stronger wave-V than males (Boston et al., 1992; Krizman et al., 2019; Lotfi & Zamiri Abdollahi, 2012; McFadden, 1998; McFadden et al., 2021). These dissimilarities could be related to anatomical differences (for instance, on averaged females have smaller and shorter cochlea and head size) or dissimilar levels of sex steroids (Liu et al., 2017; McFadden, 1998).

It is postulated that: whether androgen exposure prenatally weakens the cochlear amplifiers or estrogens play a significant role in hearing (McFadden, 2009). The evidence of the latter lay in the observation of changes in otoacoustic emission during the phases of female menstrual cycle. For

instance, more frequent spontaneous OAE and louder click-evoked OAE are found during follicular phase (when estrogen level is higher) and reduced loudness of click-evoked OAE are observed during luteal phase (when progesterone is more prominent) (Caras, 2013). Interestingly, the finding of estrogen receptors within inner ear should also be considered (Motohashi et al., 2010; Stenberg et al., 2001). It has been suggested that estrogen could help to alter cochlear homeostasis and enhance blood flow to the inner ear cells leading to a healthier hearing in females than males (review: Lien & Yang, 2021). Dissimilarities of auditory information processing on sensory level could contribute to higher cognitive processes when auditory stimuli are used in tasks for assessment of cognitive abilities.

2.1.3. Auditory scene perception

Sex related cochlear functioning and cerebral dissimilarities could result in perceptual differences of auditory scene. For instance, when auditory space is tested, females are more precise at localizing sound sources with their left ear, meanwhile males are better with the right ear (this is observed on vertical plane) (Lewald, 2004). Also, males tend to outperform females in horizontal auditory source localization tasks when stimuli are presented in distracting situations (in a so called 'cocktail party' condition): men are much more precise at pointing the location (Zündorf et al., 2011) and women are more likely to perceive auditory stimuli as being closer to a distractor (more pronounced 'pulling effect') (Lewald & Hausmann, 2013). Also, females overestimate and perceive moving sound source closer than males (Grassi, 2010; Neuhoff et al., 2009). Moreover, the perception of auditory motion with emotional background sounds demonstrates sex differences. Neuhoff et al. (2014) reported that women perceived an approaching sound to be closer with the baby cry than baby laugh on the background, meanwhile that effect was absent in men (both sounds elicited the same perception) (Neuhoff et al., 2014). Ruytjens et al. (2007) study revealed auditory attentional differences between sexes: men showed reduced activity to noise at right prefrontal cortex (that modulates responses of primary auditory cortex), on the contrary, women demonstrated higher primary auditory cortex activity to noise compared to baseline than men (Ruytjens et al., 2007). Thus, males may have better brain mechanisms to filter/resist unnecessary information. Instead, the ability to overestimate auditory scene allowed females to be more aware of the possibly dangerous environments and as a result – to react faster and increase chances of escaping the predator – the ability believed to be acquired during evolution (for review see: Caras, 2013).

2.2. Sex effect on psychiatric disorders

Psychiatric disorders have been known for many years, although the search for causes and mechanisms is still ongoing. The prevalence, age of manifestation onset and the severity of the symptoms of many psychiatric disorders differs between males and females (Bao & Swaab, 2010; Sánchez et al., 2010). For instance, male suffer more frequently from autism, attention deficit hyperactivity disorder, schizophrenia, whereas depression, anxiety disorders, anorexia nervosa are more prevalent in females (Bao & Swaab, 2010; Sánchez et al., 2010; Weafer & de Wit, 2014; Yao et al., 2014). Earlier onset, and around three times higher prevalence in females than males is found in depressive disorder (Barth et al., 2015). The onset time in schizophrenia is on average earlier in males than females; also, males suffer more pronounced positive symptoms (e.g., hallucinations), whereas females – from negative ones (like, apathy, withdrawal of social life). Moreover, the resistance to antipsychotics, severity of the symptomatology, and the consumption of psychotropic substances is more pronounced in male schizophrenia patients (Barajas et al., 2015; Bergemann et al., 2007; Markham, 2012; Sánchez et al., 2010). Interestingly, a manifestation of schizophrenia differs during different phases of lifespan. For instance, the first hit of schizophrenia in men is in puberty, when sex steroids, like testosterone, are highly elevated (Brzezinski-Sinai & Brzezinski, 2020; Markham, 2012). It is postulated that ovarian hormones act as a protective factor against schizophrenia (Brand et al., 2021; Brzezinski-Sinai & Brzezinski, 2020; Markham, 2012). Females of reproductive age with psychosis tend to be admitted to hospital more often during their menses (when estrogen levels are low), also, a second peak of the disorder is observed after menopause, yet this is when estrogen level is low (D. Jang & Elfenbein, 2019). Interestingly, lower estrogen levels are observed in both – schizophrenia female as well as in male patients (Huber et al., 2005; Kaneda & Ohmori, 2005) suggesting an influence of sex-steroids on the etiology of schizophrenia (Bergemann et al., 2007; Schroeder et al., 2016). The latter observation led to experimental therapeutic research with estrogen supplements: a few studies with female patients show improvement of their mental health by reducing psychotic and negative symptoms in schizophrenia patients (Kulkarni et al., 2015; Lascurain et al., 2020; Weiser et al., 2019).

Seeing the sex difference in psychiatric disorders rise a question if and how it reflects on parameters of electrical brain activity, related to cognitive processes. To understand the brain mechanisms of psychiatric disorders it is important to study and evaluate sex effect on the brain activity in healthy/undiagnosed population first.

2.3. Electroencephalography

Electroencephalography (EEG) is a safe and non-invasive neuroimaging method that enables to capture electrical activity arising from the human brain. Although it is one of the oldest techniques (discovered by Hans Berger in 1924) it remains an important method in neurophysiology today (Berger, 1929; İnce et al., 2020). Its advantages of a great temporal resolution and relatively low cost led to a wide usage in clinical settings as well as in research facilities. For instance, EEG is the main technique used in identifying epileptic seizures, monitoring the state of anesthesia during surgical operations, assessing sleep patterns crucial in sleep medicine (Campbell, 2009; Louis et al., 2016), and its utility does not stop here. To name a few, some of the latest implementations of EEG are Brain-Computer interface, neurofeedback, exploration of cognitive processes and application in neuropsychiatry.

The source of EEG is deriving from post-synaptic potentials of cortical pyramidal neurons, organized along cortical columns. An electrode placed on the scalp detects an electrical activity from a group of neurons. The signal consists of a summated neural activity, and in order to capture a measurable signal (1) neurons must be arranged in a parallel way; (2) they must become active at the same time; (3) the current flow in most of the neurons should be in the same direction and arising from the same part of neurons; (4) a signal must be large enough to be detected (Jackson & Bolger, 2014; Luck, 2014). More detailed description is provided in Figure 1.

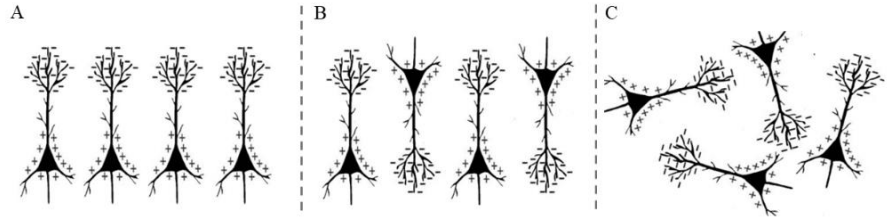

Figure 1. Signal measured at the scalp depends on the arrangement and the synchronicity of neurons. A. Neurons are arranged in a parallel radial way to the scalp and the negative signals will sum up. B. Neurons are positioned in a parallel but inverted structure, thus negative and positive signals will cancel each other out. C. Neurons arranged in random non-parallel directions resulting in a non-measurable signal at the scalp. By Jackson et Bolger, 2014.

Electrical signals that can be detected on the scalp are small – of a few microvolts, and to record an EEG, firstly, differences of two electrodes are being calculated, one of which is on the scalp and the other one, as a reference

electrode, placed on earlobe, mastoids, nose or on the center of the scalp (known as Cz electrode) (therefore, a signal is a relative value). Secondly, the signal must be amplified a million times to receive a better signal-to-noise ratio and enlarged a size of a brain signal above the size of an external and internal noise (such as electrical power supply, subjects blinking, eye movements, heartbeat etc. – all of which adds on to the final recording) (Jackson & Bolger, 2014; Stern et al., 2001).

The recording electrodes are placed on the scalp, and they are named accordingly to anatomical brain localizations, e.g., F for frontal portion of the head, P for parietal, with even numbers referring to the right side of the head, and odd − to the left. A specific electrode could capture the signal deriving not just below its place on the scalp but rather from all over the scalp, thus EEG is not the best method in assessing the exact localization of the activity (Jackson & Bolger, 2014). This dilemma is normally solved with a larger high-density number of electrodes or by combining different neuroimaging techniques, such as a structural MRI, PET exam (Chu, 2015). The number of electrodes used for EEG depends on recording facilities and the purpose – from a dual-channel EEG (used for monitoring the outcome of electroconvulsive therapy) to over 256-electrode high density EEG (applied in a scientific research settings) (Chu, 2015; Ferguson, 2008).

2.4. Event-related potentials

Event-related potentials (ERPs) are brain responses measured with a specialized technique with the help of EEG. ERPs are time-locked and averaged brain responses to the presented stimuli (also known as an event). They capture how the brain processes certain stimuli, could they be of sensory (auditory, visual, somatosensory, olfactory), motor, or cognitive origin, thus this technique is a great tool in assessing from sensory to cognitive functioning of the brain (Sur & Sinha, 2009). The ERPs are distinguished and evaluated by their latency (msec), amplitude (μV), polarity (positive or negative) (see Figure 2) and scalp distribution.

Components are named mainly after the polarity (P for positive, N for negative) and the approximate latency in milliseconds (i.e., P100, N170, P300) or, alternatively, a peaks position within the recorded waveform (N1, N2, P3, etc.). The latter naming (based on an ordinary positioning of the components in the appearance on the waveform) is now being preferable by investigators simply because the same component could appear in a wide range of time frames. For instance, P300/P3 could peak between 350 to 600 msec (not just at 300 msec, as it was first described), thus, *P3* is being used

instead of *P300*, *N2* – instead of *N200*, etc. (Luck, 2014). It is worth mentioning that some ERPs have more specific names, such as MMN (for Mismatch Negativity) or LRP (for Lateralized Readiness Potential) (Luck, 2014; Luck & Kappenman, 2012).

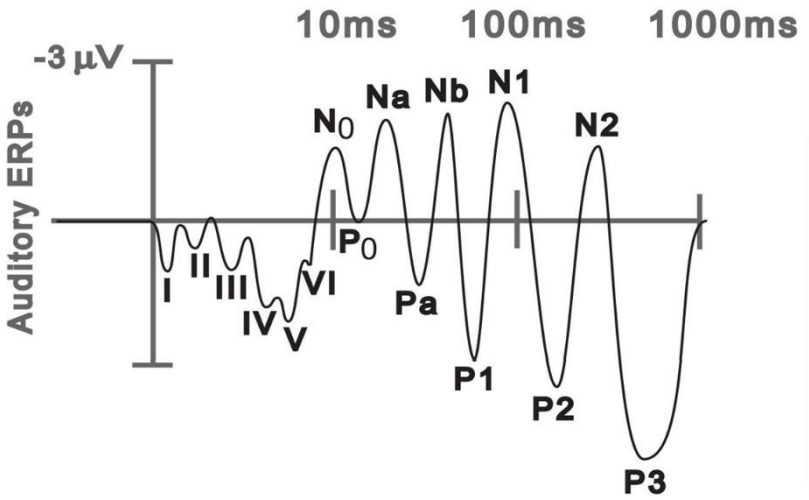

Figure 2. Auditory ERPs. Peaks I to P1/N1 that appear within the first 100 msec after the stimulus are called sensory ERPs, later appearing waves are called cognitive ERPs. Adapted from Woodman, 2010.

The source of ERPs is deriving from post-synaptic cortical pyramidal neurons when the event (stimulus) evokes a voltage fluctuation. Scalp electrodes are capturing this summed voltage; then all responses to the same type of stimulus are being averaged to produce a clear visual waveform (Kappenman & Luck, 2016).

Even though EEG is not the best method on localizing the source of the signal, each ERP has a characteristic topographical activity map. It is important to assess this during each study, as it can help to confirm and differentiate each of the ERP in the research.

The event evokes a sequence of processes in the brain – a pathway of activities in different structures of the brain. The earlier the component occurs the simpler, sensory information related processing it reflects. Later occurring changes of electrical activity represent more complex cognitive brain operations. There are two categories of components, defined by the type of brain processing:

1. Sensory or exogenous ERPs; they are related to sensory stimuli properties (hence "exogenous") and reflect early information processing emerging during the first 100 msec after stimulus

presentation. Those ERPs enable to assess functioning of sensory organs, sensory pathway (called early evoked potentials), as well as the ability of sensory gating (known as P50).

2. Cognitive or endogenous ERPs; these ERPs arise later than the sensory ones, and they reflect the way subjects brain evaluates the stimuli. Depending on the task and paradigm analysis of these components can help in evaluating memory, attention (e.g., P3), emotions and language ability (e.g., N400). Cognitive ERPs has been applied in neuropsychiatric research. (Kappenman & Luck, 2016).

This dissertation is concentrating on cognitive ERPs that have potential implications in studies with psychiatric patients that show symptoms of cognitive impairment. Auditory stimuli are one of the most frequently used stimuli in brain research in electrophysiological experiments and are advised to be implemented in clinical settings (Heinze et al., 1999). Thus, auditory N2 and P3 (the most used cognitive ERP wave) will be discussed further in more detail.

2.5. Paradigms of different stimulus probability

Cognitive EPRs are of a great use and interest in neuropsychiatry. Clinical psychiatric subjects lack some of cognitive abilities, thus it is important to use less complicated experimental procedures to evoke these components. Different sensory modality stimuli can be used to evoke the brain response, but ERP components elicited with auditory stimuli have a wider range of applications and are being recommended in clinical and research settings (Sur & Sinha, 2009).

Experimental paradigms that are being used to evoke auditory N2 and P3 can be classified by stimulus probability (Figure 3). In simple paradigms, subjects are presented with two stimuli of different tones to which subjects are instructed to react differently: (1) a tone that requires to respond (etc., press a button), and (2) the other tone that does not require any action. In an Oddball paradigm the response-required auditory stimulus (target stimulus) is presented less frequently than the other (standard) stimulus. The task is a valuable tool in evaluation of initiation and execution of response (that requires attention, working memory). In a Go-NoGo paradigm the stimulus probability is reversed, thus as the no-response tone (hence, NoGo) appears rarely, subject must put more effort to suppress the motor action, and it can help in assessing executive functioning. During the equiprobable Go-NoGo

paradigm both stimuli appear with the same probability. More details on these paradigms will be given later in the text when N2 and P3 waves are discussed.

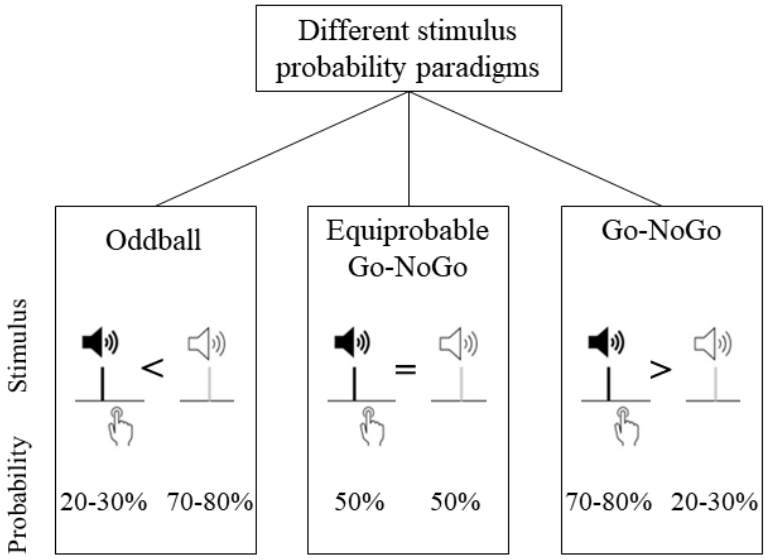

Figure 3. Different probability stimulus paradigms used to evoke N2 and P3 waves. Two tone auditory stimuli are presented to subjects in a random order: one stimulus requires a motor response (speaker symbol in black), to the other stimulus no motor action is needed (speaker symbol in white). Paradigms are classified by the probability of each stimulus.

2.6. N2/N200

N2 is a second negative ERP peak occurring at around 200-300 msec after stimulus over fronto-central electrodes (Donkers & van Boxtel, 2004; Falkenstein et al., 1991; Lavric et al., 2004; Leue et al., 2009). This potential is mainly observed during Go-NoGo, Flanker, Oddball, and other tasks when a few responses are competing and an inhibition of one of them had to be performed. Although N2 is not being studied as much as other ERPs it has some interesting origins. It is related to response conflict monitoring and inhibitory control, all of which is being processes by Anterior Cingular Cortex (ACC) (Van Veen & Carter, 2002) – a brain area found be larger in females (del Mauro et al., 2021; Lotze et al., 2019; Ruigrok et al., 2014). When in need for cognitive control ACC communicates with prefrontal brain area that alters the responses, and N2 is a neural marker of executive functioning (Espinet et al., 2012).

2.6.1. N2 in a traditional Go-NoGo paradigm

One of the main paradigms used to evoke N2 is the Go-NoGo paradigm: during it subjects must perform a response action to the Go stimulus (for instance, pressing a button) and suppress the response to the other stimulus (called NoGo) (Figure 3). In the standard Go-NoGo paradigm Go stimulus is presented more frequent than NoGo, leading the later to be more unexpected, thus more neural resources and effort is needed to withhold the prepared motor action. This is where the response conflict arises – the expected response must be suppressed in NoGo condition to perform the task correctly. Therefore, more negative (larger) N2 amplitudes are observed for NoGo trails as opposed to Go trails. For this instance, N2 represents cognitive functions of response-conflict monitoring and a need for cognitive control (Espinet et al., 2012; Nieuwenhuis et al., 2003; Waxer & Morton, 2011).

2.6.2. N2 in neuropsychiatric disorders

N2 wave has been studied in clinical populations that show symptoms of reduced self-control and executive functioning. To name a few, it has been found a reduction of amplitude or even absence of N2 component in schizophrenia patients (Kayser et al., 2001; Liang et al., 2019; O'Donnell et al., 1993, 2004; Salisbury et al., 1994). Also, a systematic review on obsessive-compulsive disorder (OCD) found greater N2 amplitudes in OCD patients vs. controls (Perera, Bailey, Herring, & Fitzgerald, 2019) and some observed smaller NoGo N2 amplitudes in OCD patients (Kim et al., 2017). A study of Leehr et al. (2018) looked at binge-eating disorder and reported an increase in N2 latency in controls with overweight but not in people with the disorder when they had to suppress the gaze at food images. The latter observation indicates a lack of compensation mechanism in people with the OCD (Leehr et al., 2018).

And although the data on psychiatric disorders is promising there is still a demand for literature, such as the effect on age, sex, methodical recommendation on N2 ERP (Tomé et al., 2015).

2.7. P3/P300

One of the widely used ERP waves in scientific and clinical studies is called P3 (also referred to as P300). As the name suggests, it is a positive peak (thus, the letter "P"), occurring at around 350-600 msec after the rare/target stimulus onset. It is considered to reflect cognitive aspects of the human brain mainly

related to Orienting Reflex, that is, an "automatic attention-grabbing response to a novel stimulus" (Barry, Steiner, et al., 2016), although there is some room for different and more detailed interpretations (Barry, Steiner, et al., 2016; van Dinteren et al., 2014). P3 can be evoked using different stimulation conditions and various paradigms and tasks, including classical Oddball, Go-NoGo, Continuous performance task, Eriksen flanker task along with others (Duncan et al., 2009). Therefore, the "meaning" of this cognitive potential can be related to the nature of the task (van Dinteren et al., 2014): it could reflect brain processing of perceptual decisions (O'Connell et al., 2012; Verleger et al., 2005), memory updating (Donchin & Coles, 1988; Nieuwenhuis et al., 2011), attention processing (Soltani & Knight, 2000) and response inhibition (Randall & Smith, 2011).

2.7.1. Theories behind P3

There are a few theories to portray the exact nature of the cognitive processes that the P3 represents (van Dinteren et al., 2014):

- *Context-updating hypothesis*. P3 represents how the expectancies related to the stimulus context is being processed and updated (Donchin, 1981; Polich, 2007). Once the sensory stimulus is presented, it is being evaluated and compared with the previous one with the help of working memory. When stimuli differ from each other, the new stimulus representation is "updated" in working memory, thus P300 is evoked. In case no changes to stimulus attribution are detected, only the sensory context is being sustained, therefore only sensory potentials are produced, P3 wave is absent.
- *Context-closure hypothesis* states that non-deviant stimuli repeated one after another form a meaningful context and once the deviant/target stimulus is presented it closes such context resulting in P3. Larger P3 amplitudes reflect greater brain activity involved with information processing that is needed for memory updating (Kenemans & Kähkönen, 2011), thus better memory performance is related to larger P3 amplitudes. In people that have a poor memory retrieval and a lack of attention (all of which is seen in schizophrenia, Alzheimer's and in people at high risk for alcoholism) the P3 amplitudes are reduced. (Hill et al., 1995).
- *Orienting response hypothesis.* Some authors believe P3 is related more to attention than memory processes. The activation of locus coeruleus-norepinephrine nervous system is involved in stimulus

evaluation leading to a perceptual decision making, thus P3 is a marker of orienting response (Nieuwenhuis et al., 2011).

2.7.2. P3 in auditory oddball paradigm

Auditory oddball paradigm is also a simple and the most used task to evoke P3. It mainly consists of two tones different in pitch that are presented in a random order. One type of stimuli is presented infrequently in a background of frequent stimuli. The subject is instructed to concentrate his attention to the rare appearing ones (called target tones) by counting or pressing a button once he have heard them, and ignore the standard ones (Goodin et al., 1994; Polich, 2007). Target tones evoke a waveform with a peak – P3 wave – that is the most prominent over parietal electrodes. This target evoked P3 is also referred to as P3b, and is elicited in experimental procedures like Oddball task, where rare target stimuli must be processed. It is a marker of context-updating operations and memory storage processes (Polich, 2007) and may reflect either memory operations associated to attentional resource activation in temporal-parietal areas (Polich, 2007) or decision making related to response execution (Verleger, 2008)

2.7.3. P3 in traditional Go-NoGo paradigm

It has been noted that during the Go-NoGo paradigm (when a rare stimulus requires suppressing a motor respond) P3 wave has slightly shorter latency and appear over fronto-central electrodes as compared to P3b wave (Barry & Rushby, 2006; Polich, 2007). That wave is defined as P3a, or novelty P300, and is recorded with a maximal positivity over frontal electrodes at about 250-280 msec latency after the rare NoGo stimuli. It reflects the engagement of the neural networks to a novel infrequent stimulus (Polich, 2007; Verleger et al., 2014). It has been linked to response inhibition processes and cancellation of the planned response (Randall & Smith, 2011). The NoGo-P3 (P3a) is generated in the frontal cortex, anterior cingulate, midcingulate cortex and insula (Gonzalez-Rosa et al., 2013; Huster et al., 2009) and is related to attention needed for stimulus evaluation.

2.7.4. P3 application in neuropsychiatric research

Auditory oddball task is being used in cognitive research as well as in psychiatric facilities, where the evoked P3 can help to assess memory, attention, and language comprehension – cognitive functions that are mainly impaired in certain psychiatric disorders. That is reflected in P3 wave

parameters: reduced P3 amplitudes in schizophrenia and other psychosis, post-traumatic stress disorder, dissociative disorder patients (Sur & Sinha, 2009), and beyond. N2 and P3 waves evoked with the Go-NoGo task serve in assessing inhibitory processes in epilepsy (Cerminara et al., 2013), drug and alcohol dependence (Oddy & Barry, 2009), depression (Bailey et al., 2014; Ruchsow, Groen, Kiefer, Beschoner, et al., 2008), obsessive-compulsive disorder (Ruchsow et al., 2007), borderline personality disorder (Ruchsow, Groen, Kiefer, Buchheim, et al., 2008), schizophrenia (Weisbrod et al., 2000) and Parkinson's disease (Beste et al., 2009). A study by Gyurak et al. (2015) found that Go-NoGo could be a tool in assessing the efficacy of antidepressant treatment (Gyurak et al., 2016). Moreover, it is found to be helpful in differentiation between schizophrenia, bipolar disorder and schizoaffective disorder (Chun et al., 2013). Thus, auditory P3 has been proposed as a potential electrophysiological biomarker in psychiatric disorders (Luck et al., 2011). The simplicity of the task procedure that enables to evoke specific ERP components, resulted in P3 to be one of the most welcome ERPs (Heinze et al., 1999; Mathalon et al., 2000).

Knowing the potential use of P3 as a biomarker it is important to evaluate all the possible compounds that could alter auditory P3 parameters. There are some data showing a significant effect of age of subjects, their cognitive abilities, personality traits, and seasonal influence, as well as methodological modifications (Bahramali et al., 1999; Ditraglia & Polich, 1991; Geisler & Polich, 1992; Polich, 1986, 1987; Polich & Hoffman, 1998; Shelton et al., 2002) and sex effect on auditory P3 is another important factor that is still understudied and debatable. Sex-related differences in auditory information processing, in auditory and cognitive abilities and in structural brain regions of parietal and temporal cortex, related to the production of auditory P3 rise a question if sex effect on this wave is prominent.

2.8. Equiprobable Go-NoGo task

2.8.1. Definition of equiprobable Go-NoGo task

Two tasks – auditory oddball and Go-NoGo – are valuable tools to assess two neural processes – initiation and execution of response (that requires attention, working memory) and the inhibition of unwanted motor action (executive functioning). When performing experiment especially in clinical populations it is important to keep a balance between the length and complexity of the tasks. It is tempting to apply as many different tasks and trials to subjects as possible, though understandably, long lasting procedures can exhaust subjects

physical and cognitive abilities and compromise the results. Barry and De Basio (2007) has proposed a modified paradigm that is a midway between the auditory oddball task (where stimulus probability is NoGo>Go) and the traditional Go-NoGo task (where stimulus probability is Go>NoGo) (Barry & De Blasio, 2013; Barry et al., 2007). It is called an auditory equiprobably Go-NoGo paradigm and, as the name suggests, is designed with equal stimuli presentation probability (Go=NoGo) (Figure 4A). With the help of this paradigm the time of the experimental procedure is shorten but the responses obtained with it share features with the neural processing that of classical paradigms. That is: the task allows the assessment of response initiation and execution and response inhibition with maximal effect.

2.8.2. ERPs evoked by the equiprobable Go-NoGo task

ERPs to Go and NoGo stimuli in the equiprobable Go-NoGo paradigm have a typical and consistent topographical appearance on the human scalp. The ERPs to the Go stimuli in this paradigm are equivalent to the processing of target stimuli during the traditional oddball paradigm. Electrical brain activity of differentiating the Go stimulus and leading to a motor response is indicated by a maximal central N2 and parietal P3 waves. The NoGo response, as in the traditional Go-NoGo paradigm, is marked by a more pronounced frontal N2 and the central P3 components (Barry & de Blasio, 2013) (Figure 4B). The cascade of neural processing of the stimuli and the response execution can be captioned with the help of evoked potentials: early potentials reflect sensory processing of the tone, then at around N1 a categorization of the Go/NoGo is processed, and it is completed at N2. At that point, depending of the response, two separate processing evens occur: to the Go stimuli a response execution is prepared leading to P3b and slow wave (SW), and to the NoGo stimuli when a response suppression is needed it is reflected in the appearance of P3a and late potential (LP) (Figure 4C), (Barry et al., 2018; Barry & de Blasio, 2013). By extracting the ERPs during the equiprobable Go-NoGo task one can evaluate the adjoined functioning processes of the brain.

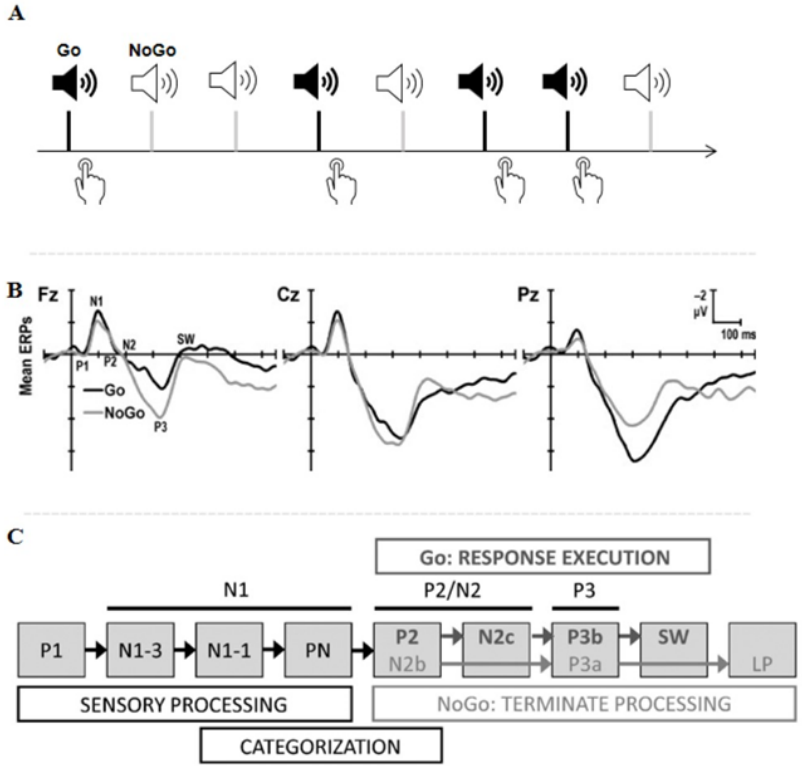

Figure 4. Auditory equiprobable Go-NoGo paradigm A. Subject is presented with two auditory stimuli in a random order: half of all stimuli are Go and the other half - NoGo stimuli. Subject is instructed to execute a response (press a button) to the appearance of the Go stimulus only. B. Mean ERPs to the Go and the NoGo stimuli over Fz, Cz and Pz electrodes illustrate a more pronounced P3 peak at frontal electrode to the NoGo stimuli, but a maximal P3 at parietal site to Go stimuli. C. A systematic representation of neural processing schema and response-related ERPs for the equiprobable Go-NoGo task – more detailed explanation is in the text. Taken and adapted from Barry et al., 2018; Barry & de Blasio, 2013.

2.8.3. Factors that affect responses of equiprobable Go-NoGo

Knowing the promising implementation of the paradigm, it is important to establish all variants that could influence the brain responses and implement normative data. It has been successfully conducted with healthy individuals of various ages (8-74 years) (Barry, de Blasio, & Borchard, 2014; Barry, de Blasio, et al., 2016; Barry & de Blasio, 2015). For instance, prolonged latencies of P3 in both conditions as well as smaller P3 and P3b that are less distinguishable between each other, along with a more frontal topographical distribution are found in older subject group (Barry, de Blasio, et al., 2016).

Also, the effect of caffeine on ERP has been assessed in some studies. The results revealed that caffeine exposure not only influenced the performance of the task (caffeine reduced reaction times and the number of omission errors), but enhanced Go-P3 in adults and in children, and N2 (in both conditions) is found more negative in children after the consumption of caffeine (Barry, de Blasio, & Cave, 2014; Barry et al., 2019). Griskova-Bulanova et al. (2016) looked at how the levels of sex steroids correlate with ERPs derived with the equiprobable Go-NoGo paradigm. They showed that longer P3 latencies were related to lower progesterone and higher estradiol levels (Griskova-Bulanova et al., 2016), indicating the possible effect of sex steroids on the ERPs. However, none of the studies to date evaluated the potential sex effect associated with behavioral and electrophysiological brain responses evoked with this task.

2.9. Types of reviews

Literature reviews can be executed in different ways, depending on the main purpose of the review: from overviewing the literature for general understanding of the topic to a more systemically performed reviews with statistical analysis of the results to draw best estimations of the effect from the available information (Grant & Booth, 2009; Sataloff et al., 2021).

Satalof et al. (2021) has separated types of review as follows (Sataloff et al., 2021):

- Systematic review. It "follows explicit methodology to answer a well-defined research question by searching the literature comprehensively, evaluating the quantity and quality of research evidence rigorously, and analysing the evidence to synthesize an answer to the research question." It aims to systematically search, appraise and synthesise research evidence about a particular question. It is done strictly according to the guidelines called Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Higgins et al., 2021) and can be classified as "systematic" only if it includes all the required items of PRISMA (Moher et al., 2009). In this way the systematic review can eliminate bias and provide validity and adequate answer to the research question.
- Meta-analysis. It is a systematic review that statistically combines the results of quantitative studies; it requires to follow guidelines of systematic review. The drawback of meta-analysis: can be inappropriate in combining studies that are not sufficiently similar.

- Literature / narrative review – identifies and sums up what was done previously. Lacks intent to maximize scope or analyse data collected; includes not just peered reviewed articles but also books, conference abstracts, etc., may not include quality assessment and might be open for bias (authors may only select articles that provide support to their views), but are good for general overview on the topic that might help to understand the general picture or serve as a steppingstone for a further systematic review.
- Rapid review provides a quick assessment of what is already known to update health policies, especially if the research is ongoing (like, in a case of Covid-19). It uses the methods for systematic reviews but is limited in search time (short duration).
- Scoping, mapping, and systematized reviews. Mapping review is used for contextualization of in-depth systematic reviews within broader literature; scoping review preliminary assesses the potential scope of available literature; systematized review attempts to include elements of systematic review but lacks the whole methodology (Grant & Booth, 2009). In general, these reviews are good for initial understanding of the topic and are great in summation of what was previously done but might oversimplify the picture and mask the variation between studies, lack explicit reporting, quality assessment, and methodology.
- Umbrella reviews – a review of other high-quality reviews (systematic and meta-analysis).
- Mixed-method reviews – a combination of a systematic review and other review.
- Others (critical review, state-of-the-art review, etc.)

Although there are some studies that specifically looked at sex factor on auditory P3 as their main aim of their research, there is still no agreement on how the sex-effect can influence parameters of auditory P3. To understand the topic in more depth it is necessary to systemically search for studies that included sex-effect in their statistical analysis and thoroughly synthesize their methodology and results. Thus, a systematic review or a meta-analysis of sex differences in auditory P3 wave is needed. This review would help to understand the topic in depth as it offers to systemize the known results with a non-bias approach.

EQUIPROBABLE GO-NOGO EXPERIMENT

3.1. Methodology

3.1.1. Subjects

Seventy-nine healthy students were recruited to participate in the experiment. The proportion of females and males were nearly equal: 40 females, aged 19-30 (median=21.97) years, and 39 males, aged 18-29 (median=22.92) years. Subjects were recruited from the student community via local advertisement. Healthy subjects were defined as participants with no reported psychiatric and neurological disorders, good self-reported general health, including hearing, and had normal or corrected to normal visual acuity. Based on self-reports, protocol required to exclude participants from the experiment when they had a history of use of psychotropic substances and other drugs, had less than 6 hours of sleep a night before the experiment and reported signs of chronic fatigue or strong emotions at the time of experiment. There were no excluded subjects from the study. Taking into consideration findings by Griskova-Bulanova et al. (2016) that sex hormones could contribute to the modulation of the brain functioning during the Go-NoGo task, the number of females was balanced according to their menstrual cycle phase. The reason for composing the female group of equal number of students at different menstrual phases was only to reflect the composition of the general public of the selected age, thus the effect of sex steroids on the brain activity will not be explored in this dissertation. Thus, there were 10 subjects of each phase of natural menstrual cycle: early follicular, late follicular, and mid-luteal phases, and 10 more females using contraceptive pills. The menstrual cycle phase was calculated for each subject individually and was based on an average duration of subject's previous three-month cycle. Knowing that the time window from ovulation and the beginning of menses is always about 14 days (Mumford et al., 2012), it was possible to assess a preliminary date of ovulation and the time frame of each phase: the beginning of the cycle was defined as early follicular phase; the last two or three days before the predicted ovulation were considered as late follicular phase, and the luteal phase was considered six to eight days after the predicted ovulation. Subjects were attributed to the phase group randomly and participated in the experiment only once.

Part of the data for the female sample (27 participants) was used from the study focusing on the effects of sex steroid hormones on the Go-NoGo paradigm (Griskova-Bulanova et al., 2016). The study was approved by the

Lithuanian Bioethics Committee No. 59, issued on 2007-12-22 and all subjects gave their written-informed consent.

3.1.2. Paradigm and stimuli

The auditory equiprobable (50/50) Go-NoGo task was used in the experiment (Figure 4A). The task was following Barry et al. (2007) where two types of auditory stimuli were presented and subjects required to respond to the Go stimuli and withhold the response to the NoGo stimuli (Barry et al., 2007). Participants received 150 auditory tones in total, 75 of each type: 1000 Hz and 1500 Hz, 50 msec duration, 5 msec rise/fall times. Tones were presented in a random order with a fixed stimulus onset asynchrony of 1100 msec via headphones at 60 dB SPL.

3.1.3. Experimental procedure

Subjects were seated in a comfortable chair in a dark and soundproof room where they were introduced and familiarized with both auditory tones prior to the experiment. A response keyboard was presented in front of participants, and they were instructed to respond by pressing a button to the tones with the target frequency. Target tone for each participant was randomly assigned to 1000 Hz or 1500 Hz, interchangeably between subjects. Participants were asked to concentrate, have their eyes open and fixate at the fixation cross on the computer screen in front of them. The task required to respond as accurate and as quick as possible.

3.1.4. EEG recording

The EEG was recorded with the EEG device (ANT Neuro, the Netherlands) using WaveGuard EEG cap with Ag/AgCl electrodes with a gain of 50 mV/V. Reference was taken from averaged mastoid electrodes; the ground electrode was attached at around Fz site. The impedance was kept below 5 kΩ. The recordings were digitized at 512 Hz, the usable bandwidth was DC to ~ 138 Hz.

3.1.5. Data pre-processing

Data preprocessing was done off-line in EEGLAB for MATLAB© (Delorme & Makeig, 2004). Power-line noise was removed using multi-tapering and Thomas F-statistics implemented in CleanLine plugin for EEGLAB. The epochs containing muscle artifacts were manually rejected. Eye-movement

and blink correction was performed using Independent Component analysis (ICA). Data were filtered at 0.1-25 Hz. Epochs of 600 msec were created starting at 100 msec prior to stimulus onset and lasting for 500 msec post-stimulus onset, separately for Go and NoGo conditions, and baseline-corrected to the mean of the pre-stimulus period. After the data pre-processing, minimum 60 responses were averaged for each participant in each condition.

3.1.6. Data extraction

Event-related potentials (ERPs) and behavioral performance were of interest in this research.

Two ERP components were evaluated: N2 and P3. The N2 was defined as a second negative peak after N1 appearing in the timeframe of 180-270 msec and P3 was defined as a positive peak within 240-400 msec after the stimulus. The N2s and P3s were measured as peak values at three midline (Fz, Cz, and Pz) electrodes. Peaks in response to the Go condition were further referred to as the Go-P3 and Go-N2; peaks in response to the NoGo condition were further referred to as the NoGo-P3 and NoGo-N2.

Additionally, response times (RTs) to the Go stimuli as well as response accuracy in both – the Go and the NoGo – tasks were calculated. The response accuracy was expressed in percentage of correct responses.

3.1.7. Data statistical analysis

Statistical assessment was performed in STATISTICA, version 10 (Stat Soft, Inc., 2011). For statistical testing of the amplitude and latency data a repeated measures ANOVA (RM-ANOVA) was performed, with TASK (Go vs. NoGo) and SITE (Fz, Cz, Pz) as within-subject factors and SEX (males vs. females) as a between-subject factor. The interaction of TASK*SITE was done to confirm the expected effect of the stimulating condition, whereas the main effect of SEX and interaction of SEX*TASK was focused on. $P<0.05$ were regarded as significant for RM-ANOVA effects. Significant main effects and interaction effects were followed up with post hoc pairwise comparisons adjusted using a Bonferroni correction (corrected p values reported).

RT was evaluated using an unpaired two-sample t-test. As the accuracy did not fit normal distribution, the Kolmogorov-Smirnov Test was used to assess accuracy differences between groups. Spearman correlation was performed to estimate the relationship between response times and the amplitude/latency

values of the ERP components (N2 and P3) measured from the maximal amplitude site. P<0.01 were regarded as significant.

3.2. Results

3.2.1. Behavioural data

Mean RT to the Go stimuli was 379.8 msec (SE 3.32), mean percentage of correct responses in the Go condition was 96.7 % (SE 0.48) and mean accuracy in the NoGo condition (no responses) was 96.91 % (SE 0.43). The mean RT did not differ between males and females ($F(1,77) = 0.03$, $p = 0.87$). Males responded on average in 378.8 msec (SE 8.99) and females in 380.8 msec (SE 9.0). Males were more accurate than females in the Go condition ($p < 0.025$), but the accuracy was comparable between sexes in the NoGo condition ($p > 0.10$). Response accuracy in the Go condition was 97.7 % (SE 0.7) for males and 95.6 % (SE 0.63) for females and in the NoGo condition – 97.4 % (SE 0.48) and 96.4 % (SE 0.7) respectively.

3.2.2. ERP data

The mean peak amplitudes and peak latencies and corresponding standard errors of mean (SE) values are presented in Table 1. Grand averaged waveforms from Fz, Cz, and Pz electrodes are presented in Figure 5. N2 and P3 latencies and amplitudes in the Go and the NoGo conditions for males and females are presented in Figure 6 and Figure 7. The results for each parameter of N2 and P3 are expanded and presented separately.

3.2.2.1. N2 amplitudes

There was a significant interaction of TASK*SITE ($F(2,154) = 11.436$, $p < 0.001$, partial $eta^2 = 0.13$) for N2 amplitudes, with the most negative amplitudes over Fz in both conditions and significantly more negative amplitudes obtained over Pz in the NoGo as compared to the Go ($p < 0.001$). The effect of SEX was not significant for N2 amplitudes ($F(1,77) = 0.015$, $p = 0.90$, partial $eta2 < 0.001$), showing N2 amplitudes to be comparable in males and females. The interaction of SEX*TASK was not observed ($F(1,77) = 0.64$, $p = 0.43$, partial $eta2 = 0.01$).

3.2.2.2. P3 amplitudes

A significant TASK*SITE interaction was observed for P3 amplitudes (F (2,154) =5 1.755, $p < 0.001$, partial $\eta^2 = 0.40$). Post hoc analysis confirmed the highest P3 amplitudes at Pz electrode in the Go condition and at Cz – in the NoGo condition (for all effects $p < 0.001$). The significant effect of SEX was found for P3 amplitudes (F (1,77) = 6.027, p = 0.02, partial $\eta^2 = 0.07$), revealing higher P3 amplitudes in females. A nearly significant effect of TASK*SEX interaction (F (1,77) = 3,477, p = 0.06, partial $\eta^2 = 0.04$) indicated the SEX effect could be condition dependent. Indeed, there were no differences in P3 amplitudes between males and females in the NoGo condition (p = 1.0) but higher averaged P3 amplitudes were revealed in females during the Go condition (p = 0.017).

Table 1. Mean values and SE of N2 and P3 latencies (msec) and amplitudes (μV) for males(M) and females(F) over Fz, Cz and Pz electrodes.

			N2		**P3**	
			Go	NoGo	Go	NoGo
			Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Latency	Fz	M	243.19 (5.75)	226.63 (4.90)	327.57 (5.76)	320.04 (5.89)
		F	247.22 (5.68)	237.70 (4.83)	342.68 (5.69)	339.65 (5.81)
	Cz	M	238.70 (4.90)	221.26 (5.19)	328.51 (6.11)	312.96 (5.13)
		F	247.27 (4.84)	235.22 (5.12)	347.71 (6.04)	330.79 (5.07)
	Pz	M	214.39 (6.12)	215.54 (6.02)	319.09 (5.71)	310.66 (5.62)
		F	237.30 (6.04)	228.34 (5.94)	344.92 (5.64)	320.31 (5.55)
Amplitude	Fz	M	-0.92 (0.53)	-1.31 (0.52)	2.44 (0.60)	4.86 (0.73)
		F	-2.28 (0.52)	-1.77 (0.51)	4.52 (0.59)	6.15 (0.72)
	Cz	M	0.50 (0.64)	0.26 (0.59)	4.94 (0.82)	7.74 (0.88)
		F	-0.07 (0.63)	0.06 (0.58)	7.59 (0.81)	8.41 (0.87)
	Pz	M	1.16 (0.57)	-0.18 (0.49)	6.32 (0.70)	5.64 (0.62)
		F	2.20 (0.56)	0.94 (0.48)	10.32 (0.69)	7.38 (0.61)

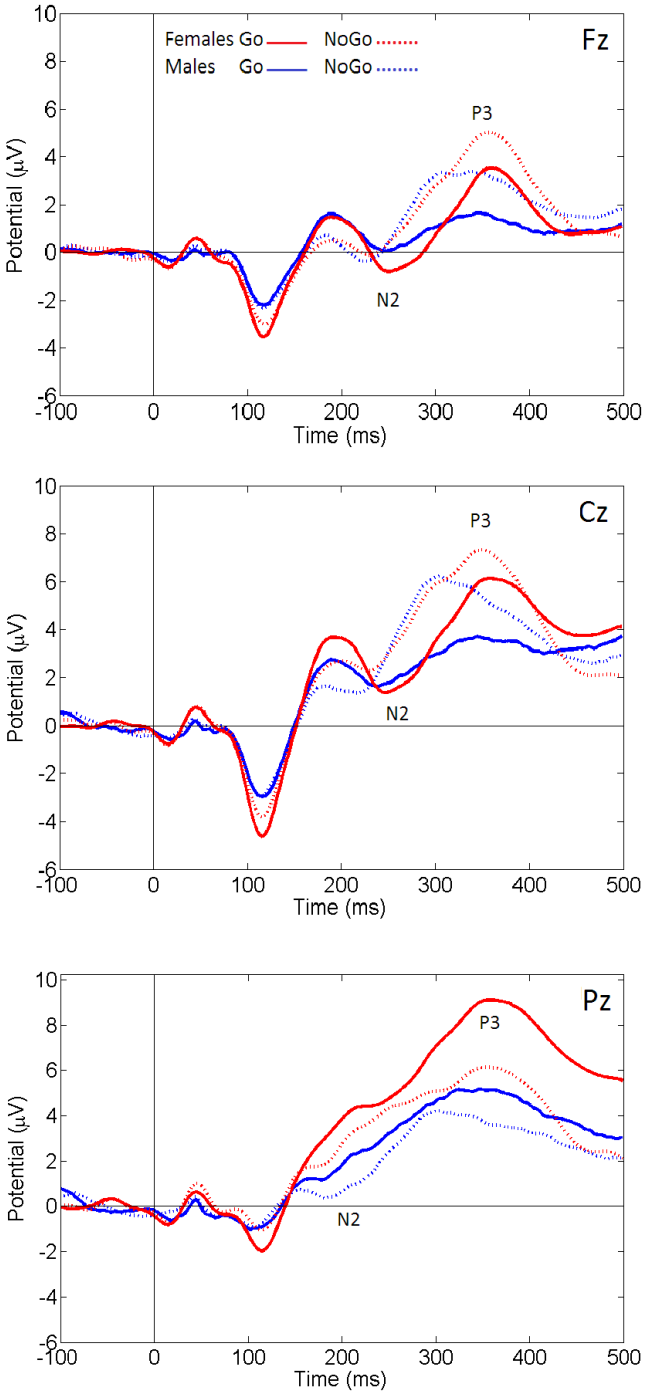

Figure 5. ERP waveforms in males (blue) and females (red) over Fz, Cz and Pz electrodes to Go (solid lines) and NoGo (dotted lines) stimuli.

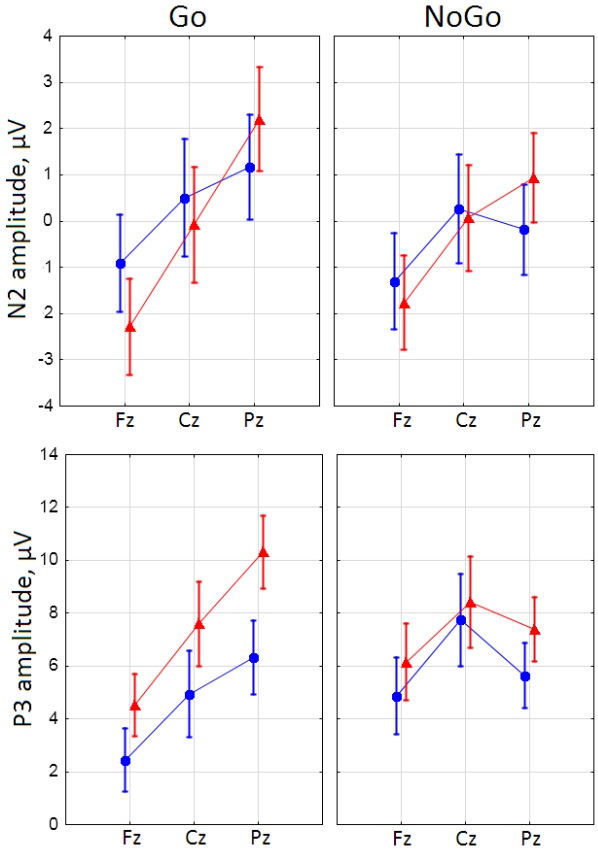

Figure 6. N2 and P3 amplitudes with SE in the Go and the NoGo conditions for males (blue dots) and females (red triangles)

3.2.2.3. N2 latencies

For N2 latencies, the interaction of TASK*SITE was non-significant (F (2,154) = 2.767, p = 0.07, partial eta2 = 0.07). RM-ANOVA indicated a significant effect of SEX for the N2 latencies (F (1,77) = 4.416, p = 0.04, partial eta2 = 0.05), which were longer in females independently of the task (as confirmed by the absence of SEX*TASK interaction (F (1,77) = 0.02, p = 0.89, partial eta2 = 0.00)).

3.2.2.4. P3 latencies

The significant TASK*SITE interaction emerged for P3 latencies (F (2,154) = 3.420, p = 0.04, partial η^2 = 0.04): larger values were found in the Go

condition as compared to the NoGo over Cz and Pz ($p < 0.001$). Also, the SEX factor had a significant impact on P3 latencies ($F(1,77) = 12.570$, $p < 0.001$, partial $\eta^2 = 0.14$). It was observed that females exhibiting slower P3 response. This effect was independent of the condition, as confirmed by the absence of SEX*TASK interaction ($F(1,77) = 0.21$, $p = 0.64$, partial $\eta^2 = 0.00$).

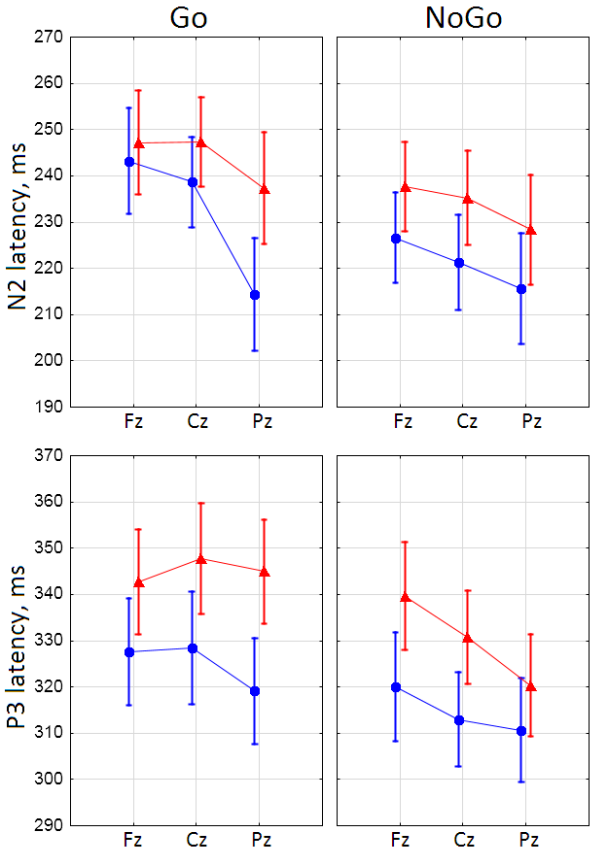

Figure 7. N2 and P3 latencies with SE in the Go and the NoGo conditions for males (blue dots) and females (red triangles)

3.2.3. Correlations

The scatterplots of Go and NoGo P3 amplitudes against the behavioral data in male and female groups are presented in Figure 8. There was a negative relationship between the Go-P3 (over Pz) and response times but only in the female group. Meanwhile, a negative correlation between the reaction times and P3 amplitudes (over Cz) in the NoGo condition was prominent in both groups, showing that higher NoGo-P3 amplitudes were related to faster responses to the Go stimuli. Similar results were observed for the relationship

between P3 and the accuracy – Go-P3 (over Pz) and accuracy negatively correlated only in females, whereas NoGo-P3 (over Cz) and accuracy positively correlated in both groups.

No significant correlations were observed between the behavioral data and N2 amplitudes or latencies in both conditions.

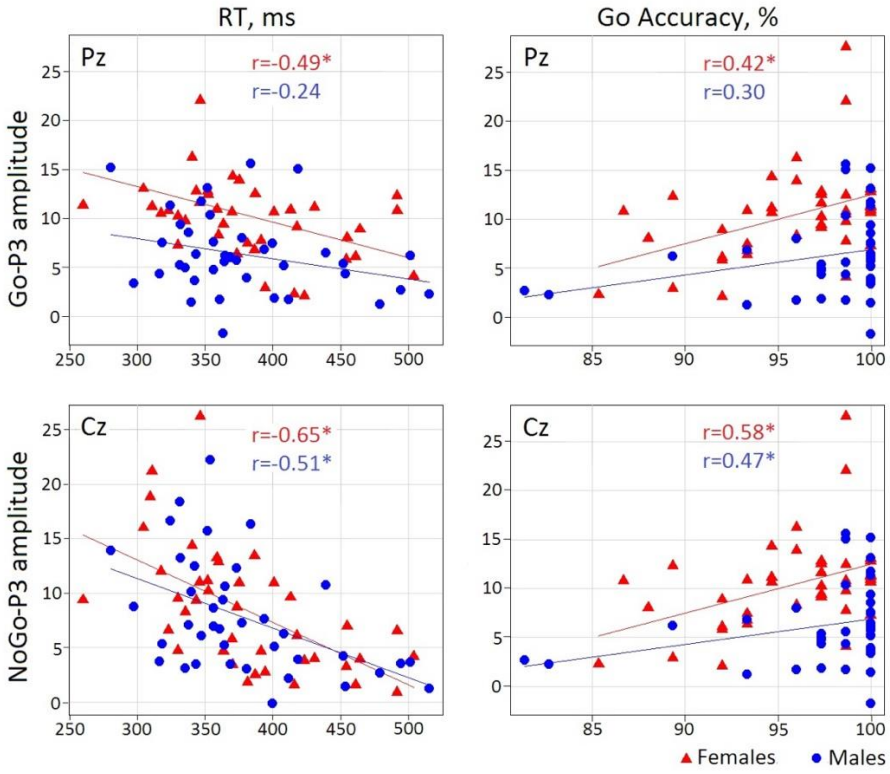

*Figure 8. Correlation of Go (over Pz) and NoGo (over Cz) P3 amplitude with reaction time (RT) and Go accuracy in males (blue) and females (red) * P<0.01.*

3.2.4. Brief Summary of Results

The main purpose of this experiment was to evaluate sex effects on brain responses (marked as N2 and P3 electrophysiological components) when performing the auditory equal probability Go-NoGo paradigm. During the paradigm subjects required to execute a button-press response to the target stimuli (Go) and inhibit the response to the other stimuli (NoGo). It was expected to find a specific topographical distribution of N2 and P3 components, that is: a posterior N2 and a centroparietal P3b for the Go stimulus (when effortful motor response is executed), and a frontal N2b and

frontocentral P3a for the NoGo (Barry & de Blasio, 2013; Barry & Rushby, 2006; Folstein & van Petten, 2008; Huster et al., 2013). The expected effect of different tasks was shown by the TASK*SITE interaction for both N2 and P3 amplitudes (higher activity over centro-frontal electrodes in NoGo condition and over centro-parietal ones in Go condition) that proved the existence of two distinct N2 and P3 for each of the conditions, in line as described by Barry et al. (2007).

In terms of sex effect on N2 and P3, a significantly higher P3 amplitudes and longer P3 latencies were found in females than in males. There were no significant differences for N2 amplitudes when sex was concerned, although females exhibited longer N2 latencies. The response times were indifferent between males and females, whereas a slightly lower Go accuracy was observed in females. In terms of processing pathways of two different conditions in the context of sex, lower P3 amplitudes were found in males during the Go condition, but no difference between sexes in the NoGo condition. Also, higher Go-P3 amplitudes (from Pz) were associated with faster reaction times on the Go condition in females only, but a negative interaction between NoGo-P3 amplitudes (from Cz) and the response times was observed in both sex groups.

The results suggest that sex is an important factor and should be taken into consideration when evaluating Go-P3 amplitudes, P3 and N2 latencies during the auditory equiprobable Go-NoGo paradigm.

SYSTEMATIC REVIEW OF SEX EFFECTS ON AUDITORY P3

4.1. Methodology

4.1.1. Data search methods

A systematic review was conducted for peer reviewed scientific papers using two databases: the PubMed and ScienceDirect. The search keywords included "Auditory AND (P3 OR P300) AND (sex OR gender)" and papers published between 01/01/2000 and 12/04/2021 were selected. The article titles and summaries where then scanned for chosen inclusion criteria and when not enough information was given in the summary, the methods section of the paper was studied further.

The search methods were discussed with the Vilnius University librarians to capture findings more accurately.

4.1.2. Inclusion criteria

The articles were selected when they met the inclusion criteria defined as follows:

a) The study reported data on healthy subjects 18 years of age and older.
b) Paradigms with pure tone auditory stimuli were applied.
c) Paper was an original research article.

Only studies that were published in English were included. When papers were not accessible in full-text or some necessary data was not given, the authors were contacted to retrieve the missing information. Additionally, original articles that did not come up on the specific search but were cited by the already included studies and met the inclusion criteria were selected.

All papers fitting the inclusion criteria were than scanned if sex effect on auditory P3 was assessed in their study.

4.1.3. Extracted data

The following data was extracted from each of the selected study:

- Publication year.
- Number of subjects, including number of males and females.
- Mean age or age range in years.
- Study paradigm and target probability.
- Recording sites.

- Type of response (button press or counting of target stimuli).
- Stimulus intensity.
- Inter-stimulus interval.
- Recording reference.
- Amplitude assessment method.

4.1.4. Assessment of risk of bias

To assess the risk of bias related to study design, methodology, result representation, and discussion of the findings, nine items of risk of bias were chosen (Table 2). Items to evaluate major risk of bias were selected according to the Cochrane Handbook (Ryan et al., 2013). The scale was adapted to capture major sources of bias: selection bias, reporting bias and statistical bias. For instance, bias in sampling illustrates group compatibility in age and sample size, also whether menstrual cycle in females was considered. Bias in methodology refers to transparency of description of experimental paradigm, measuring procedures of P3 amplitude and latency, also, reporting of the results, interpretation of findings and statistical power.

Each study was given a score on every individual item from 0 (stating that the study does not provide the data on the item) to 1 (the information is given in full). When information was insufficient, inconclusive and some aspects were missing, a study was scored 0.5 on that individual item. Finally, score for each item was summed up, and studies were further categorized depending on the final score as having a low or high risk of bias. A study with a total score of 7 or above was regarded as having a low risk of bias.

Table 2. Description of risk of bias items

Item	Label	Description
1	Age compatibility	Were male and female groups compatible in age? Was the p value provided?
2	Size compatibility	Were male and female groups compatible in sample size? Was the p value provided?
3	Compatibility on sex hormones	Was the level of sex hormones and/or phase of menstrual cycle assessed in female subject?
4	Paradigm description	Was the description of the paradigm used provided in full, and replicable (type of paradigm, stimuli characteristics, presentation ratio, inter-stimulus interval, response type)?

5	ERP measurement	Was the description of the way ERPs were measured provided in full (data extraction, artefact reduction, peak establishment)?
6	Selective reporting	Were means and standard deviation provided for healthy/control males and females?
7	Sex acknowledgement	Were results related to sex effect discussed and possible reasons attributed?
8	Statistical power	Was sample size of at least 10 people?
9	Statistical evaluation of sex factor	Were the corresponding p values provided for the sex effect on latency and/or amplitude?

4.2. Results

4.2.1. Methodological characteristics

Search steps are presented in Figure 9. In sum, 2844 articles were found. Once the duplicates, non-English written papers and articles that did not meet the inclusion criteria were removed, in total of 152 papers complied with the search inclusion requirements. They were screened further for data on sex effect. As 114 articles did not present any data on gender/sex effect on auditory P300/P3 they were removed from the final list, leaving the final number of reviewed original research articles to 38 (Figure 9).

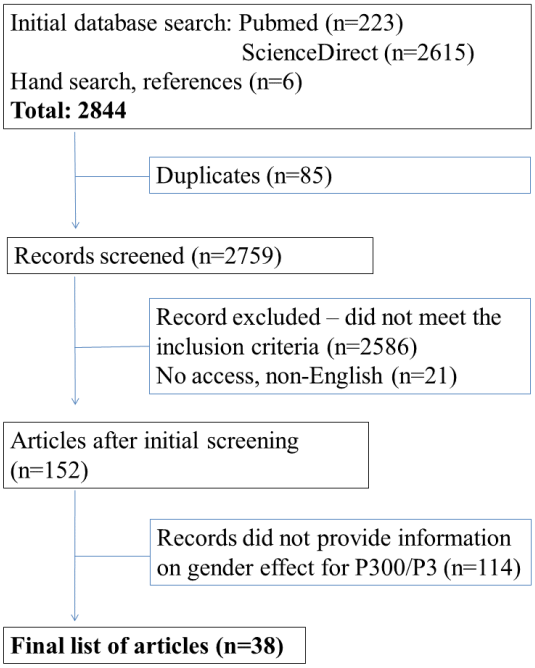

Figure 9. Search process for studies that looked at sex/gender effect on auditory P3 for systematic review.

4.2.2. Overview of the selected articles

All the related information on the results for males vs females for P3 parameters, along with the demographic and methodological information are presented in Table 3. Demographic information includes the size of sample, number of males and females separately and their age (mean or range); then the results of sex effect on P3 amplitude or latency along with other kind of assessment such correlations are presented; methodological information includes information of design of paradigm, stimuli presentation probability for standard and for target; behavioral response type and other details; in notes – the main aim of the study is stated.

Firstly, the selected studies were reviewed to estimate how many reported sex-related differences as one of the primal study purposes. Assessment of sex-related aspects was stated as the main aim in 13 studies out of all 38 (Andersson et al., 2011; Araki et al., 2006; Hirayasu et al., 2000; Jausovec & Jausovec, 2009; Karakaş et al., 2006; Kudo et al., 2004; Melynyte et al., 2017; Reese & Polich, 2003; Shelton et al., 2002; Sumich et al., 2014; Sumich,

Kumari, Gordon, et al., 2008; Tsolaki et al., 2015; Wang et al., 2014). The remaining 25 studies reported sex effect in their results, but it was not the primary topic.

When looked at methodological aspects of the studies (such as paradigms used, mode of response required, sample size and the way the P3 was measured), they were found to vary. Most of the articles employed cross-sectional design and ERPs were evaluated once during the whole experiment. The most common task was the two-tone oddball paradigm where subjects required to respond by pressing a button, although other methodological aspects such as stimulus presentation probabilities, stimulus features and inter-stimulus interval settings, as well as acquisition methods for P300 varied in these studies (Table 3). Sample sizes in the included studies varied from 10 to 1318 subjects, although the number of males and females was mostly equal. Most of the studies measured amplitude as a peak from the baseline, with only a few estimating it as mean values or a peak-to-peak. The reference electrodes for EEG recording were mainly mastoids or attached to earlobes.

As not in all the papers both amplitude and latency were evaluated, results on these parameters will be presented separately. Also, some studies focused on sex-related differences on the correlational level – assessing relationship between parameters of P3 wave and some physiological or psychological variables (for instance, correlation with P3 latency and age (Araki et al., 2006), P3 and personality traits (Mucci et al., 2005; Sumich et al., 2014; Sumich, Kumari, Dodd, et al., 2008; Sumich, Kumari, Gordon, et al., 2008). In these articles, no data on direct comparison between males and females was performed and descriptive statistics of the parameters was absent.

Table 3. Demographics, methodological information, and results of P3 amplitudes and latencies in males and females for all selected studies. More details in text.

	Sample size; M/F; Age (years)	**Results**			**Methodology**				
		Amplitude	**Latency**	**Other[a]**	**Sites**	**Paradigm; stimuli presentation, % (std/target); response type**	**ISI; stimuli features (std/target); SPL**	**Recording reference; peak measured**	**Notes**
Andersson et al., 2011	36; 18/18; 22 ± 3.4 (18-25)	Larger in females	n.s.	-	Fz, Cz, Pz	*3-Modality attend/ignore*; equal probability; press button	10-20 sec; 1000 Hz; 70 dBA	Mastoid; mean	Chemosensory habituation, sex effect
Araki et al., 2006	70; 41/29; 35.5 ± 10.6 (HC)	-	-	n.s.c. of P3b latency ∗ age and P3a latency ∗ age (HC males and females)	Pz (P3b, oddball), Cz (P3a, 3-tone)	*Oddball:* 2-Tone: 85/15; 3-Tone: 70/15/15; press button	1.5 sec; 1000/2000 Hz; 75 dB	Earlobes; peak-to-peak	Sz; latency prolongation with age, sex effect
César et al., 2010	34; 20/14; 18-39 (HC)	n.s.	n.s.	-	Cz, Pz	*Oddball:* 80/20; raise hand	0,7 sec; 750/2000 Hz; 70 dB	Earlobes; peak-to-peak	P300 in Down's syndrome
Force et al., 2008	36; 21/15;	Larger in females	n.s.	-	Fz, Cz, Pz	*Two-dimensional dichotic listening task:*	1.12–1.53 sec; higher pitch set:	Earlobe (left); peak-to-peak	Genetic liability for Sz and BD

	47.5 ± 15.1 (HC)					80/10/10 (target-infrequent pip to attended ear; unattended deviant – infrequent pip to unattended ear); press button	1600/2400 Hz; lower pitch set: 800/1200 Hz; 96 dB		
Fridberg et al., 2009	52; 24/28; 40.7 ± 11 (HC)	n.s.	n.s.	-	Pz	*Oddball:* 85/15; press button	-; 1000/1500 Hz; 86 dB	Nose; mean	BD; influencing factors of ERPs
Godleski et al., 2010	112; 67/45; 19 ± 1.4	n.s.	n.s.	-	Fz, Cz, Pz	*Auditory perseveration task:* 40/40 + 20 white noise; press button to high or low tone	2.5 sec; 1000/500 Hz; 70 dB	Mastoid; baseline-to-peak	Hostile attribution - P300 amplitude = allocation of cognitive resources or enhanced "attending" to salient stimuli.
Golob et al., 2007	66; 32/34; 20.8 (young HC); 75.1	Larger in females	n.s.	-	Pz	*Oddball:* 80/20; press button	2.5 sec; 1000/2000 Hz; 70 dB	Mastoid; baseline-to-peak	MCI and Alz – 5-year follow up; P300-cognitive function of outcome

	(elderly HC)								
Gurrera et al., 2005	43; 28/15; 27.1 ± 9.2	Larger in females at F4 and T5	n.s.	n.s.c. latency ∗ neuroticism and latency ∗ extraversion in males or females	F3, Fz, F4; T5, Pz, T6 and Cz	*Oddball:* 85/15; count	1.3 sec; 1000/1500 Hz; 97 dB	Earlobes; baseline-to-peak	Personality traits
Hirayasu et al., 2000	84; 42/42; 38.6 ± 19	Larger in females	n.s.	s.c. (+) latency ∗ age only in > 30 y old males at Pz; latency slope for >30y olds s. steeper in males than females; s.c. (-) amplitude ∗ age only in males >30y old at Pz.	T5, T6, Pz	*Oddball:* 80/20; count	1.7 sec; 1000/2000 Hz; 75 dB	Earlobes; baseline-to-peak	Sex effect of latency with age
Higashima et al., 2002	36; 21/15; 25.8 ± 4.8;	n.s.	n.s.	-	Fz, Cz, Pz, T5 and T6	*Oddball:* 80/20; press button	1,25 sec; 1000/2000 Hz; 70dB	Earlobes; baseline-to-peak	Sz

	20–37 (HC)								
Jausovec & Jausovec, 2009	60; 30/30[b]; 20.5	Larger in females	n.s.	-	Fz, Cz, Pz, Fp1, Fp2,F3, F4, F7, F8, T3, T4, T5, T5, T6, C3, C4, P3, P4, O1, O2	*Unattended 3-Tone condition*: 33/33/33. *Oddball*: 70/30; count	3-4 sec; 1000/1500/2000 Hz; 1000/1500 Hz; 65 dB	Mastoid; peak-to-peak	Sex effect on efficiency of visual vs auditory event-categorization processes
Jaworska et al., 2013	43; 20/23; 36.5 ± 9.8 (HC)	Larger P3a/b in females	n.s.	-	C3/4 (P3a), P3/4 (P3b)	*3-Tone:* 80/10 + novel non-target sound 10; count	1 sec; 1000/700 Hz; 65-75 dB	Mastoids; baseline-to-peak	MDD, responders vs non-responders to antidepressants. P3 = basic attentive processes
Karakaş et al., 2006	42; 20/22; 19–39	Larger in females	-	Higher target-evoked in females, but higher standard-evoked in males.	Fz, Cz, Pz	*Oddball*: 80/20; count	-; 1000/2000 Hz; 65 dB	Earlobes; -	Gamma response status and sex effect on P300

Kudo et al., 2004	22; 11/11; 27.8 ± 3	n.s.	-	-	Fz, T3, Cz, T4, Pz	*Selective attention task*: left ear short tone, 35%; left long, 15%; right short, 35%; right long, 15%; press button	0.75 sec; 1000/2000 Hz; 75 dB	Earlobes; peak-to-peak	Effect of corollary discharge on P300; sex effect
Light et al., 2015	753; 371/382; 38.6 ± 13 (HC)	Larger in females	-	-	Cz	*Duration-deviant oddball*: 90/10; ignore	-; 1000 Hz; 50/100 msec; 85 dB	Mastoid (left); mean	Validation of P3a in Sz.
Lindín et al., 2004	25; 11/14; 20.8, 18–30	Larger in males at Pz	-	n.s. but smaller P300 amplitude in the first block of stimuli than in the second in females; n.s. but smaller P300 amplitude in the second block than in the first bloc in males.	Fz, Cz, Pz	*Oddball*: 80/20; press button	0.9 sec; 1000/1200 Hz; 85 dB	Nose; baseline-to-peak	Oddball methodology effect on P300

Mavrogiorgou et al., 2002	17; 11/6; 36 ± 9 (HC)	HC - n.s. (P3a and P3b)	HC - n.s. (P3a and P3b)	-	-	*Oddball*: 80/20; press button	1.5 sec; 500/1000 Hz; 80 dB	Cz; baseline-to-peak	OCD
Mayaud et al., 2013	10; 5/5; 36.3 ± 12.2; 24–58	-	n.s.[e]		Fz, Cz, Pz, Oz, PO3, PO7	*Oddball:* 85/15; count	-; 1000/500 Hz; -	Mastoid (right); -	EEG recording methods
Melynyte et al., 2017	79; 39/40[c] 18–29	Larger Go P3 amplitude in females	Longer Go and NoGo P3 latencies in females	-	Fz, Cz, Pz	*Go/NoGo*: 50/50; press button	1.1 sec; 1000/1500 Hz; 60 dB	Mastoids; baseline-to-peak	Sex effect on Go (motor response execution) and NoGo (response inhibition)
Mobascher et al., 2010	1318; 558/760; 36.6 ± 13.5			P300 GFP: s. effect of sex and s. sex ∗ site interaction	Fz, Cz, Pz	*Oddball:* 80/20; button press	1.75 sec; 1500/2000 Hz; 70 dB	FCz; baseline-to-peak	Effect of smoking
Mori et al., 2007	70; 39/31; 39.0 (HC)	n.s.	n.s.	s.c. (+) latency ∗ age in males in all sites, but only Pz for females	Fz, Cz, Pz	*Oddball*: 80/20; count	-; 0.5 Hz; 1000/2000 Hz and vice versa; 70 dB	Earlobes; baseline-to-peak	Sz: illness duration and latency
Mucci et al., 2005	43; 18/25;	-	-	s.c. paranoia scale ∗ topographic	P3b - parietal,	*3-Tone*: 52/26 + 22 non-target rare; press button	1.5-2 sec; 3000/1000 Hz +	Earlobes; baseline-to-peak	Psychotic experience in healthy

	22.9 ± 2.6			al distribution of P3a in females only: higher scores predicted more leftward shift; high-psychotic vs. low-psychotic: a leftward shift in females only	P3a - anterior		6000Hz; 60 dB		and response lateralizatio n
Ozcan et al., 2016	21; 12/9; 18–65 (HC)	n.s.	n.s.	-	Pz	*Oddball:* 83/17; press button, count	2 sec; 1000/1500 Hz, 80 dB	Earlobes; peak-to-peak and baseline-to-peak	OCD
Ozgürdal et al., 2008	54; 32/22; 27.7 ± 4.6 (HC)	Larger in females at Pz	-	-	Fz, Cz, Pz	*Oddball*: 76/24; press button	1.5 sec; 500/1000 Hz; 83 dB	Mastoids, baseline-to-peak	Sz and prodromal phase

Reese & Polich, 2003	24; 12/12; 18–24	*Matching task:* n.s. main effect. Larger in HR females than HR males at Pz. *Location task:* n.s. main effect. Larger in females for the harder tasks	n.s.		Fz, Cz, Pz	*Matching task:* 80/20; press button. *Location task:* 80/10/10; press two different keys for each target tone Easy and hard conditions in both tasks	-; range 500-3900 Hz; 70–90 dB	Earlobes; baseline-to-peak	Alcoholism risk (low risk, high risk) and task effect (modality, difficulty, sex)
Roser et al., 2008	20; 10/10 (3 groups); 28.2 ± 3.1	n.s.	-	-	Fz, Cz, Pz	*Choice reaction task: 50/50; press one of two buttons depending on tone; stimuli presented in variable ISIs*	2.5–7.5 sec; 1000/2000 Hz; 80 dB	FCz; baseline-to-peak	Effect of Δ9-tetrahydrocannabinol and cannabis extract on P300
Schiff et al., 2008	68; 34/34; 20–70	Larger in females	n.s.	n. s. c. sex ∗ age on latency and amplitude	Pz	*Oddball*: 80/20; count in first part and move finger in second	1.2–2.5 sec; 1000/2000 Hz; 110 dB	Earlobes; baseline-to-peak	Effect of aging on P300

Shelton et al., 2002	442; 213/229; M: 24 ± 6, F: 24 ± 6	Larger in males in winter and summer	n.s.	The greatest difference in latencies during winter: in female shorter than in males	Cz	*Oddball*: 85/15; count	1 sec; 1000/2000 Hz; 80 dB	Mastoid; baseline-to-peak	Seasonal patterns, sex and modality effect on P300
Sumich, Kumari, Heasman et al., 2006	70; 35/35; 34.3 ± 10.7 (HC)	n.s.	-	-	Lateral/ medial sites; Fz, Cz, Pz	*Oddball*: 80/20; press button	1 sec; 500/1000 Hz; 75 dB	Mastoid; baseline-to-peak	Subclinical depression
Sumich et al., 2014	40; 20/20; M: 20 ± 2, F: 19 ± 1	-	-	n.s.c. amplitude ∗ PSQ with sex.	F7, F3, F8,F4, T5, P3, T6, P4	*Oddball*: 80/20; press two buttons	1 sec; 500/1000 Hz; 75 dB	Mastoid; baseline-to-peak	Paranoia, suspiciousness in healthy; sex effect
Sumich, Kumari, Dodd, et al., 2008	18; 5/13; 28.3 (HC)	-	-	s.c. (-) in males only: schyzotypy ∗ NoGo P300 (at frontal) and schyzotypy Go P300 (oddball) (at central sites)	F3, F4, Fz, C3, C4, Cz, P3, P4, Pz	*Go/NoGo* (response to high tones). *Oddball* (response to low tones); 80/20; press button	1 sec; 2000/1000 Hz; 65 dB	Mastoid; baseline-to-peak	Sz and siblings; NoGo P300 – executive function.

Sumich, Kumari, Gordon, et al., 2008	72; 36/36; M: 37.8 (18–57), F: 35 (20–68)	-	-	s.c. (-) in females only: PI P300 amplitude at right-anterior and UE ∗ P300 amplitude at right-anterior electrodes	F7, F3, F8, F4, T3, C3, T4,C4, T5, P3, T6, P4	*Oddball*: 80/20; press button	1 sec; 500/1000 Hz; 75 dB	Mastoid; baseline-to-peak	Paranormal idealization and unusual experience in healthy; sex effect
Szinnai et al., 2005	16; 8/8[d]; M: 28 ± 5, F: 25 ± 4	n.s.	n.s.	-	Fz, Cz, Pz	*Oddball*: 80/20; press button	-; 1200/800 Hz; -	Mastoid; baseline-to-peak	Effect of water deprivation on cognitive-motor performance
Tsolaki et al., 2015	44; 21/23; 33 ± 4.3 (young); 67 ± 2.7 (elderly)	n.s.	n.s.	Elderly males have more frontal distribution of P300 amplitude than elderly females	Pz	*Oddball*: 80/20; press button	2 sec; 250/4000 Hz; 75 dB	Cz; -	Aging and sex effect on brain source localization

Turetsky et al., 2015	649; 330/319; 38 ± 12 (HC)	n.s.	n.s.	-	Pz	*Oddball*: 85/15; press button	-; 1000/1500 Hz; -	Mastoid (left); baseline-to-peak	Utility of P300 as a Sz endophenotype
van der Stelt et al., 2005	8/6 (young HC), 10/4 (older HC): 22.5 ± 2.0 (19–25); 34.1 ± 10.9 (24–57)	n.s. on the P300 amplitude at Pz.	-	-	Pz	*Oddball*: 91.5/8.5	1.5 sec; 1000/1064 Hz; 85 dB SPL	Mastoid (right); mean	P300 in patients at high imminent risk for Sz
Wang et al., 2014	28; 14/14; 24.8 (HC)	HC: P300 n.s. P3d larger in females	n.s.	-	Fz, Cz, Pz	*Oddball*: 80/20; press button	1–1.5 sec; 1000/1600 Hz; 65 dB	Mastoid (left); baseline-to-peak	Migraine patients; cognitive performance ; sex effect
Yu et al., 2005	101; 36/65; 38 ± 13 (HC)	HC: Larger in females at Pz	n.s.	n.s. sex effect on latency slope	Fz, Cz, Pz	*Oddball*: 15.4; count	0.75 sec; 1000/2000 Hz; 80 dB	Earlobes; -	Sz; effecting factors of P300 in Chinese population

Abbr.: HC – healthy controls; M – males; F – females; s. – significant difference; n.s. – no significant difference; s.c. – significant correlation ((+) – positive, (-) – negative); n.s.c. – no significant correlation; Sz – schizophrenia; BD – bipolar disorder; MDD – major depressive disorder; MCI – mild cognitive impairment; Alz – Alzheimer's disease; OCD – obsessive compulsive disorder; HR – healthy subject with high-risk of alcoholism; PI – paranormal ideation; UE – unusual experiences; PSQ – paranoia/suspiciousness questionnaire; GFP – global field power, ISI – inter-stimulus interval.

[a]- Other than direct comparison of sex-related results of P3 amplitude or latency (correlation with age, personality traits, effect of methodology)

[b]- subjects matched by intelligent, emotional intelligent and personality traits.

[c]- female subjects balanced by menstrual phase and hormonal contraceptive usage.

[d]- female subject during follicular phase.

[e]- differences were calculated from means and SD provided in the article.

4.2.3. Effect of sex on P3 amplitude

Thirty one out of 38 studies assessed P3 amplitude and 13 of these reported larger P3 amplitudes in females than in males (Andersson et al., 2011; Force et al., 2008; Golob et al., 2007; Gurrera et al., 2005; Hirayasu et al., 2000; Jausovec & Jausovec, 2009; Jaworska et al., 2013; Karakaş et al., 2006; Light et al., 2015; Melynyte et al., 2017; Ozgürdal et al., 2008; Schiff et al., 2008; Yu et al., 2005). Also, there was one study that reported a larger P3d parameter (an amplitude as a difference wave between the target and standard responses) in females (Wang et al., 2014). The stronger activation generated by the auditory stimuli in females was primarily observed over Pz site – the electrode where auditory stimuli elicit the most prominent response (Hayashida et al., 1992). On the other hand, the sex effect could be spread to the fronto-central regions (i.e., Cz and Fz), and lateralized locations (i.e. F3/4, C3/4, T5/6, P3/4) as shown in several other studies (Gurrera et al., 2005; Jausovec & Jausovec, 2009).

Contrarily, two studies presented reversed findings, showing higher amplitudes over Pz and Cz locations in male subjects in comparison to females (Lindín et al., 2004; Shelton et al., 2002). Furthermore, one study reported higher source intensity (but not amplitude) in males (Tsolaki et al., 2015). There were 16 papers that found no significant differences on P300 amplitude between males and females (César et al., 2010; Fridberg et al., 2009; Godleski et al., 2010; Higashima et al., 2002; Kudo et al., 2004; Mavrogiorgou et al., 2002; Mori et al., 2007; Ozcan et al., 2016; Reese & Polich, 2003; Roser et al., 2008; Sumich et al., 2006; Szinnai et al., 2005; Tsolaki et al., 2015; Turetsky et al., 2015; van der Stelt et al., 2005; Wang et al., 2014). Also, one study reported significant effect of sex without specifying further (Mobascher et al., 2010).

The authors reporting higher P3 amplitudes in males than females admitted the contradiction of their findings to the existing studies and discussed that this might be due to a small sample size and the lack of statistical power (Lindín et al., 2004; Shelton et al., 2002). The remaining papers that failed to demonstrate sex effect argued that the results were related either to the difference in the nature of the task (Tsolaki et al., 2015), the lack of sufficient statistical power (Kudo et al., 2004), or did not discuss it (César et al., 2010; Fridberg et al., 2009; Godleski et al., 2010; Higashima et al., 2002; Turetsky et al., 2015). Several studies argued that anatomical and functional sex dissimilarities could impact the representation of brain responses, therefore, additional variables might mask the differences (Araki et al., 2006; Mori et al., 2007; Sumich et al., 2014; Tsolaki et al., 2015). It is important to mention

that 5 studies out of 16 where no significant sex effect on P3 amplitude was observed had very small sample sizes, groups consisting of 10 or less subjects of each sex, (Mavrogiorgou et al., 2002; Ozcan et al., 2016; Roser et al., 2008; Szinnai et al., 2005; van der Stelt et al., 2005), thus they could potentially be underpowered.

According to the authors that reported stronger responses in females than males, the differences were related to the anatomical dissimilarities (Hirayasu et al., 2000; Tsolaki et al., 2015), hormonal status (Reese & Polich, 2003) and differences present due to functional nature of the task (Jausovec & Jausovec, 2009; Karakaş et al., 2006). Interestingly, the potential effect of sex hormones was controlled for in only two studies (Melynyte et al., 2017; Szinnai et al., 2005) - the menstrual cycle phase was considered when recruiting the subjects.

4.2.4. Effect of sex on P3 latency

P3 latency was evaluated in 24 out of 38 studies. Apart from one paper that reported longer latencies in females than in males (Melynyte et al., 2017), all found no sex-related effect on P3 latencies (Andersson et al., 2011; César et al., 2010; Force et al., 2008; Fridberg et al., 2009; Godleski et al., 2010; Golob et al., 2007; Gurrera et al., 2005; Higashima et al., 2002; Hirayasu et al., 2000; Jausovec & Jausovec, 2009; Jaworska et al., 2013; Mavrogiorgou et al., 2002; Mayaud et al., 2013; Mori et al., 2007; Ozcan et al., 2016; Reese & Polich, 2003; Schiff et al., 2008; Shelton et al., 2002; Szinnai et al., 2005; Tsolaki et al., 2015; Turetsky et al., 2015; Wang et al., 2014; Yu et al., 2005).

The similarity of P3 latencies between both sexes appears to be a consistent finding, despite the variability of the stimulation settings and paradigms that were applied in the study. Nevertheless, it should be noted that only one (our) study (Melynyte et al., 2017) employed an equiprobable Go/NoGo task which was not used by any of others and included young female subjects balanced by their menstrual cycle phase – the equal number of females in follicular, ovulation and luteal phase and those on steroid contraceptive pills.

Of the included studies, one paper reported a more pronounced latency lengthening with age (Hirayasu et al., 2000), whereas another study found a positive correlation between age and P3 latency at Fz, Cz and Pz sites in males, and only at Pz location in females (Mori et al., 2007); two studies failed to find any relationship between age and sex (Araki et al., 2006; Schiff et al., 2008). Therefore, the observed results are unlikely due to the potential age influence.

4.2.5. Risk of bias

Most of the studies had methodological limitations that prevented from a careful evaluation of sex-related effects on P3 amplitude and latency, such as, small sample sizes (Mayaud et al., 2013; Szinnai et al., 2005), no control for menstrual cycle phase, use of sex steroid contraception and the level of sex steroid hormones; insufficient presentation of methodological details (Ozgürdal et al., 2008); assessment of only one measure (amplitude or latency) of the P3; insufficient information on sex-related results without statistical details or discussion (Jausovec & Jausovec, 2009; Mobascher et al., 2010; Shelton et al., 2002) or only presentation of correlational patterns without direct comparison between sexes (Sumich et al., 2014).

Table 4. Selected studies evaluated for each Risk of bias

Article	1	2	3	4	5	6	7	8	9	Total score
Andersson et al., 2011	1	1	0	1	1	1	1	1	1	8
Araki et al. 2006	1	1	0	1	1	0	1	1	0	6
César et al., 2010	1	1	0	1	1	1	0	1	1	7
Force et al., 2008	0	1	0	1	1	0	0	1	1	5
Fridberg et al., 2009	0	1	0	0.5	1	0	0	1	0	3.5
Godleski et al., 2010	0	1	0	1	1	0	0	1	0	4
Golob et al., 2007	0	1	0	1	1	0	0	1	0	4
Gurrera et al., 2005	1	0	0	1	1	1	1	1	1	7
Hirayasu et al., 2000	1	1	0	1	1	1	1	1	1	8
Higashima et al., 2003	0	1	0	1	1	0	0	1	0	4
Jausovec and Jausovec, 2009	0	1	1	1	1	0	1	1	1	7
Jaworska et al., 2013	0	1	0	1	1	0	1	1	1	6
Karakaş et al., 2006	0	1	0	0.5	0.5	1	1	1	1	6
Kudo et al., 2004	1	1	0	1	1	1	1	1	1	8
Light et al., 2015	1	1	0	0.5	1	0	0	1	0	4.5
Lindín et al., 2004	0	1	0	1	1	1	0	1	1	6
Mavrogiorgou et al.	0	1	0	1	1	0	0	0	0	3
Mayaud et al., 2013	0	1	0	0.5	0.5	0	0	0	0	2
Melynyte et al., 2017	1	1	1	1	1	1	1	1	1	9
Mobascher et al., 2010	0	1	0	1	1	0	1	1	1	6

Mori et al., 2007	1	1	0	1	0.5	1	1	1	1	7.5
Mucci et al. 2005	0	1	0	1	1	0	1	1	0	5
Ozcan et al., 2016	0	1	0	1	1	0	0	0	0	3
Ozgürdal et al., 2008	0	1	0	1	1	0	0	1	1	5
Reese and Polich, 2003	0	1	0	0.5	1	0	1	1	1	5.5
Roser et al., 2008	0	1	0	1	1	0	0	0	0	3
Schiff et al., 2008	1	1	0	1	1	1	1	1	1	8
Shelton et al., 2002	1	1	0	1	1	0	1	1	1	7
Sumich et al., 2006	1	1	0	1	1	1	1	1	1	8
Sumich et al. 2014	1	1	0	1	1	0	1	1	0	6
Sumich, Kumari, Dodd, et al. 2008	0	0	0	1	1	0	0	0	0	2
Sumich, Kumari, Gordon, et al. 2008	1	1	0	1	1	0	1	1	0	6
Szinnai et al., 2005	1	1	1	1	0.5	1	1	0	1	7.5
Tsolaki et al., 2015	1	1	0	1	0.5	1	1	1	1	7.5
Turetsky et al., 2015	0	1	0	0.5	1	0	0	1	1	4.5
van der Stelt et al., 2005	0	0	0	1	1	0	0	0	0	2
Wang et al., 2014	1	1	0	1	1	0	1	1	0	6
Yu et al., 2005	1	0	0	1	0.5	1	1	1	1	6.5

The assessment of the included studies for the risks of bias is presented in Table 4. Only 13 studies out of 38 could be categorized as having low risk of bias. Six of them reported larger amplitudes in females (Andersson et al., 2011; Gurrera et al., 2005; Hirayasu et al., 2000; Jausovec & Jausovec, 2009; Melynyte et al., 2017; Schiff et al., 2008), six studies found no differences (César et al., 2010; Kudo et al., 2004; Mori et al., 2007; Sumich et al., 2006; Szinnai et al., 2005; Tsolaki et al., 2015) and one of 13 studies observed higher amplitudes in males (Shelton et al., 2002). P3 latencies were shown to be alike between sexes in most of the studies (Andersson et al., 2011; César et al., 2010; Gurrera et al., 2005; Hirayasu et al., 2000; Jausovec & Jausovec, 2009; Shelton et al., 2002; Tsolaki et al., 2015) apart from our study (Melynyte et al., 2017) that observed longer latencies in females. The results do not seem to be consistently related to any methodological differences (paradigm, recording reference or amplitude assessment method).

4.2.6. Brief Summary of the Results

This systematic review was conducted to assess studies that reported sex-related effects on the auditory P3, evoked by simple auditory paradigms. The main results of the review are as follows:

- Comparable P3 latencies between males and females.
- Sex effect on P3 amplitudes is not fully clear but cannot be neglected: half of the studies observed larger P3 amplitudes in females, the other half reported no sex related differences; only one study observed greater P3 amplitude in males.
- Sex related differences were reported over centro-parietal topographic locations, suggesting the effect to be on P3b component.

DISCUSSION

One of the main aims of the dissertation was to assess the sex effect on N2 and P3 parameters in the promising task that could be applied in psychiatric settings – the auditory equiprobable Go-NoGo. The results show longer latencies of N2 and P3 and larger amplitudes of P3 in females as compared to males; N2 amplitudes were comparable between sexes. Importantly, the effect on P3 was mostly driven by significantly higher P3 amplitudes in females during the Go condition. The other aim of the dissertation was to systematically review scientific papers that assessed auditory P3 component in connection with sex-related effect. The review revealed that half of the studies found higher P3 amplitudes in females, and the other half found no sex effect on this parameter; P3 latencies were mainly comparable between sexes.

The results of the experiment and the systematic review indicate that the sex effect on parameters of N2 and P3 is present. The discrepancies in the results, especially for P3 amplitudes, suggest involvement of possible confounding factors. Further, the results of each component – N2 and P3 – will be discussed separately.

5.1. Effects of sex on N2

There is a limited number of studies that looked at sex effect on auditory N2. The N2 in the Go-NoGo task potentially represents neural processes of the monitoring of response conflict (Folstein & van Petten, 2008; Nieuwenhuis et al., 2003). Our study revealed a lack of difference in N2 amplitudes between males and females, and it was consistent with some previous reports where oddball paradigm was applied (Hirayasu et al., 2000; Schiff et al., 2008). On the other hand, there are some studies that reported higher N2 amplitudes in males; that was found with the classical auditory oddball (Karakaş et al., 2006) and passive auditory oddball paradigm (Nagy et al., 2003) and passive listening task (Berchicci et al., 2020). Also, N2 amplitudes were reported to be higher in females in a task with monaural and binaural conditions (Carpenter et al., 2001). Meanwhile, the latencies of N2 in both experimental conditions of Carpenter et al. (2001) were longer in females, and these findings are contradicting in comparison to results reported in other studies that show no sex effect on N2 latencies (Hirayasu et al., 2000; Nagy et al., 2003; Schiff et al., 2008). A probable involvement of the level of progesterone in the bloodstream was suggested as on a trend level Go-N2 latencies were reported to be longer in female subjects with higher progesterone levels

(Griskova-Bulanova et al., 2016), partly supported by the findings of Walpurger et al. (Walpurger et al., 2004).

In studies that employed other sensory modalities and different tasks, e.g., with a continuous performance task (Omura & Kusumoto, 2015) and a modified Ericson Flanker task (Clayson et al., 2011), larger N2 amplitudes in males than females were reported. In an experiment with emotional background conducted by Ramos-Loyo et al. (2016), higher NoGo-N2 amplitudes were found in females (Ramos-Loyo et al., 2016). Therefore, it is uncertain at this point to draw any firm conclusions of sex related differences on N2 parameters, and more extensive studies in this field should be conducted.

5.2. P3 and the sex effect

The neural processing of response inhibition to the NoGo stimuli in the equiprobable Go-NoGo task revealed comparable NoGo-P3 amplitudes in males and females. On the other hand, when the effortful response preparation is required to the target / Go stimuli, the Go-P3 amplitudes were higher in females. This finding is in line with the results of half of the studies with the classical oddball or novelty paradigms as revealed in the systematic review. Half of the selected reviewed studies failed to find differences in P3 amplitudes between sexes (with the classical oddball or auditory discrimination task), thus it is important to overview certain aspects that could help to understand the result discrepancies and the underlying causes of sex-related effects. Those aspects can be categorized as follows:

- Brain structural and functional dissimilarities.
- The effect of sex steroids.
- Methodological differences and aspects related to it.
- Demographic differences.

These aspects will be further discussed in more detail.

5.2.1. Neuroanatomical differences

The way the brain processes stimuli is influenced by its structure and physiology, and as a result it is reflected in electrophysiological parameters. The Go stimuli (similarly to classical auditory oddball paradigms) evoke activation in parietal cortex, whereas the activation by the NoGo events is mainly restricted to the frontal cortex and the involvement of the parietal cortex is low (Laurens et al., 2005).

It has been demonstrated that the thickness and brain wiring of the human cortex differ between males and females (Ingalhalikar et al., 2014; Ritchie et al., 2018; Sowell et al., 2007). Moreover, two distinct sex-related patterns of hemispheric connectome have been reported (Ingalhalikar et al., 2014; Ritchie et al., 2018). The existing evidence of functional connectivity of the brain suggests higher intrahemispheric connectivity in males, while females exhibit stronger interhemispheric connectivity (Ingalhalikar et al., 2014). Higher cognitive functions and interhemispheric transfer time is closely related to the morphology of the corpus callosum (Hinkley et al., 2012; Schulte et al., 2004). A positive relation between the size of the corpus callosum and P3 amplitudes and a negative with P3 latency was reported (Polich & Hoffman, 1998). To note, females tend to have larger callosal commissure (Allen et al., 1991; Steinmetz et al., 1992). A correlation of P3 amplitudes to the rare-target stimuli and the volume of parietal lobe (Ford et al., 1994) was shown. Again, the grey matter volume of parietal lobe is shown to be thicker in females (Im et al., 2006; Luders et al., 2006; Lv et al., 2010; Ritchie et al., 2018; Sowell et al., 2007). Similarly, the absence of differences between males and females in the NoGo condition in the equiprobable Go-NoGo task as observed in this thesis could be related to the similar structural composition of the frontal cortex in both males and females (Sowell et al., 2007).

All above mentioned does support the sex-specific findings of the P3, but the question remains open why half of the reviewed studies did not observe the same results. The structural dissimilarities could be related to the differences in topographic appearance of the P3. As found in the systematic review, most studies reported the greater activation over Pz electrode, although some other studies showed that this effect could be extended to the fronto-central regions and lateralized brain locations (Gurrera et al., 2005; Jausovec & Jausovec, 2009). For instance, in difficult task conditions (when subjects had to press the response key opposite the location of the tone) P3 amplitudes in males showed a less increase in amplitudes from the frontal to parietal sites (Reese & Polich, 2003). Also, Tsolaki et al. (2015) reported that females had stronger response intensity in the frontal lobe, whereas males had it in the temporal lobe. A study by Mucci et al. (2005) also reported a topographical difference between P3 in males and females (Mucci et al., 2005). These observations of sex-related brain differences and recording aspects could be a possible cause of the discrepancy of P3 results that were found in some of the reviewed studies. It is difficult to draw final conclusions on the settings where measured P3 wave is more prone to sex effect, however

it raises a question if males and females use different neural processes to execute the same task-related function.

5.2.2. Functional differences

The anatomical differences are closely related to functional discrepancies; therefore, functional brain dissimilarities could not be overlooked. In this instance, the auditory system is more sensitive in females as opposed to males, and that is shown from birth to the elderly age (for review see: Caras, 2013; McFadden, 2009), on the other hand the allocation of attention to the stimuli is more pronounced in males than females (Nagy et al., 2003). Distinct brain connectome in males and females could be attributed to different cognitive abilities found in averaged populations, such as spatial processing and motor functions: sensorimotor speed is more efficient in males (as their intrahemispheric interaction), whereas females possess better functions needed for integration of both hemispheres, such as attention, word or face recognition and memory (Ingalhalikar et al., 2014).

ERP components appear in a certain temporal sequence, one after another; thus, it is plausible that earlier sensory and preattentional levels of processing of the auditory stimuli could affect the appearance of the cognitive ERPs, such as P3. For instance, it has been shown that the change in P3 amplitudes with the use of psilocybin is in line with the change in earlier potentials such as N1 (Bravermanová et al., 2018; Karakaş et al., 2006). Unfortunately, the number of studies that investigated sex-effect on N1, P2 or N2 ERP components is very limited, and the results are inconclusive. Some studies found no sex-related differences in N1 amplitudes and latencies (Carpenter et al., 2001; Jausovec & Jausovec, 2009; Kudo et al., 2004; Lijffijt et al., 2009; Schiff et al., 2008) and N2 amplitudes (Hirayasu et al., 2000; Wang et al., 2014), meanwhile some studies reported higher N1 and N1/P2 slopes in females (Berchicci et al., 2020; Lijffijt et al., 2009; Oliva et al., 2011) or more negative N2 amplitudes in males (Nagy et al., 2003). Therefore, future studies should evaluate the earlier ERP components so that the sex related processes could be identified and understood.

5.2.3. The effect of sex steroids

Sex hormones are crucial in coordinating the development and functioning of the reproductive system in males and females, but their effect extend beyond. These steroids interact with the neurochemicals, leading to the changed morphology and neurophysiology of the brain (Barth et al., 2015; Forger et

al., 2015; Larson, 2018).

Although, the effect of different neurochemical substrates on P3 is well documented (Frodl-Bauch et al., 1999), the results of the systematic review revealed that the number of studies considering the effect of sex hormones is very limited. A study by Szinnai et al. (2005) included females during their early follicular phase (when the level of sex hormones is expected to be the lowest), and they found no differences in P3 amplitudes as compared with males. When P3 was assessed in females during different phases of the menstrual cycle, some authors reported the P3 amplitudes to be lower when estrogen levels were high (Aydin et al., 2004), although other studies showed no effect of menstrual cycle phase on P3 parameters (Braverman et al., 2009; Ehlers, Phillips, & Parry, 1996; Fleck & Polich, 1988; Walpurger et al., 2004). Also, Braverman and colleagues (2009) reported that levels of testosterone negatively correlated with P3 latencies (but not the amplitudes) in those males that were between 30-49 years old (Braverman et al., 2009). Anderer et al. showed that a combined medication of synthetic sex hormones (estradiol and progestin) in females shortened P3 latencies and increased P3 amplitudes (Anderer et al., 2003, 2004). Importantly, the concentration of neuroactive steroids – chemicals that are the precursors of sex hormones (like, dehydroepiandrosterone), are found to negatively correlate with P3 latencies in both males and females (Braverman et al., 2009). Finally, in the study of the same auditory equiprobable Go-NoGo paradigm with the naturally cycling females, the higher level of estradiol was related to longer P3 latencies in the Go condition, but lower progesterone was related to longer latencies of P3 in the NoGo condition, suggesting that both steroids pay a significant and specific role depending on the task (Griskova-Bulanova et al., 2016). Thus, individual levels of sex hormones might be the cause of the potential sex differences in P3 parameters.

5.2.4. Task effect

The incompatible P3 amplitude results of the systematic review could also be related to the variability of task settings leading to possibility of distinct functional outcomes in males and females. For instance, P3 amplitudes elicited by target stimuli were higher in females than males, but standard-evoked P3 amplitudes were higher in males (Karakaş et al., 2006). Moreover, Lindin et al. (2004) reported smaller P3 amplitudes in the first block of stimulation in females, whereas in males the reduction was found in the second block (Lindín et al., 2004). In our equiprobable Go-NoGo experiment larger P3 amplitudes for females than males were only in Go condition, but

not in NoGo. When two types of tasks were given to the subjects – one difficult (e.g., press right button when stimulus is presented on the left) and the other easy – males exhibit lower P3 amplitudes in the difficult task (Reese & Polich, 2003).

While performing the equiprobable auditory Go-NoGo task females had higher amplitudes of Go-P3 than males. Also Go-P3 amplitudes correlated with RT in female subjects only. These findings suggest that for females faster responses require more neural recourses. In the Go-NoGo tasks without social aspects females tend to perform better for impulse control but RT times are indifferent between sexes (Sjoberg & Cole, 2018). This goes in hand with the results of our experiment, where males and females responded at a similar speed, but males performed the task less accurately. In equiprobable Go-NoGo task, as opposed to a classical Oddball task, both stimuli are equally expected. Males and females engage different neural processes of cognitive control (Li et al., 2006, 2009). That might have caused involvement of different sex-specific strategies for executing the response, and that was reflected in dissimilar Go-P3 parameters.

It is important to mention that reports using different paradigms and even sensory modalities found sex differences in ERPs. To mention a few, smaller amplitudes and/or longer P3 latencies in males than females were found when performing a visual Stroop task (Shen, 2005), a modified visual oddball paradigm with emotional stimuli (Yuan et al., 2008), a visual object recognition task (Steffensen et al., 2008), a phoneme discrimination task (Aerts et al., 2015). Moreover, a study with chemosensory stimuli reported higher P3 amplitudes in females than in males (Andersson et al., 2011).

The above mentioned suggest that task specific functioning in males and females should not be overlooked in other studies as well.

5.2.5. Methodological and demographical aspects

It is known that the brain undergoes maturation in the frontal and parietal cortices until the late twenties (Sowell et al., 2003), therefore, the age of subjects should be considered as a potential cause of mismatched results. For instance, Sumich et al. (2012) reported a different maturation of ERPs in boys and girls, such as, adolescent girls had more prominent and bilaterally distributed anterior P3 than the same age boys (Sumich et al., 2012). Also, shorter P3 and N2 latencies related to older age in young adult males but not in females (Hirayasu et al., 2000). Moreover, a topographical P3 differences were observed in elderly subjects: males had more frontal distribution of P3 amplitude than elderly females (Tsolaki et al., 2015). When looking at the

reviewed studies it is unclear if the maturation effect alone could be the cause of the sex differences in P3 parameters. The results of studies related to sex effect on ERPs that employed young samples varied: some found higher amplitudes in females (Andersson et al., 2011; Jausovec & Jausovec, 2009; Schirmer et al., 2007), others – in males (Shelton et al., 2002), or no sex-related differences (Kudo et al., 2004; Mori et al., 2007; Szinnai et al., 2005).

As well as age, other individual factors might have contributed to the results on P3 amplitudes and latencies. Although Gurrera et al. reported no significant correlation between P3 parameters and personally traits (Gurrera et al., 2005), Sumich and colleagues found sex-specific relations between P3 amplitude and paranormal ideation and unusual experience in female subjects only (Sumich, Kumari, Gordon, et al., 2008). All this suggest that some personality differences and believes could lead to sex-related differences.

Overall, the confounding seasonal attribution in context of sex effect on P3 is credible, as there is a well-documented sex-related differences in the seasonal mood change (Jang et al., 1997; Lucht & Kasper, 1999) as well as a fluctuation of sex hormones such as testosterone within different seasons (Demir et al., 2016; Moskovic et al., 2012). Shelton et al. reported higher P3 amplitudes during winter and summer seasons in male subjects, also the greatest dissimilarities in P3 latencies were found during winter season (shorter in females) (Shelton et al., 2002). Seasonal fluctuation was reported to affect P3 amplitudes in earlier studies as well (Polich & Geisler, 1991). Although the P3 latencies were mainly comparable between sexes in all but one (our) study (Melynyte et al., 2017), it is worth mentioning a study by Uvais et al. (2020): in young Indian subjects longer latencies of auditory P3 in females than males, but no sex-related differences in the amplitudes (Uvais et al., 2020) were observed. Therefore, the ethnicity effect on P3 could also be a potential question.

5.3. Limitations

5.3.1. Equiprobable Go-NoGo

Several limitations of the experimental part of this thesis are worth mentioning. First, subjects were not evaluated on their current emotional state, paranormal believes or personality traits in general; the psychological health was not assessed in detail and relied on self-reports. All subjects were university students of similar age and education level and were highly motivated to take part in the experiment (the participation was not paid for, and all subjects were on a volunteering basis), thus the results of the

experiment should be generalized for young, educated population only. Future studies should include more variable and broader populations in terms of age, educational level, personality trails, and hormonal levels in both sexes. It is recommended that earlier components of ERPs (N1, P1, P2) would also be taken into consideration.

5.3.2. The systematic review

One of the aims of this review was to conduct a full-scale meta-analysis on this topic. Unfortunately, it was not possible to achieve due to fact that mean values of P3 parameters for each group in most of studies were not presented, and the attempt to contact the corresponding authors of those studies was fruitless.

5.4. Follow-up studies

Since the publication of the experimental results presented in this thesis, the main developer of the equiprobable Go-NoGo paradigm (prof. RJ Barry) has acknowledged the possibility and importance of sex variant in the studies and has address this issue in some of his further studies (de Blasio & Barry, 2020; Karamacoska et al., 2019); authors increased number of female subjects in their samples to compensate for the possible sex-effect (more specifically, to control for the variability of different phases of menstrual cycle and the levels of female sex hormones related to it). The systematic review presented in this thesis also received some attention by the scientific community. The article was cited to discuss the limitations of the study results (Coppens et al., 2021; Stevens et al., 2019), or support the reasons for matching subject for sex (Chi et al., 2019; Sharma et al., 2019). Also, two more studies that cited the review have looked at sex as a factor in their studies (Krepel et al., 2020; Uvais et al., 2020). Above mentioned indicates the interest of the topic in the scientific community.

CONCLUSIONS

- Larger P3 amplitudes were observed in females as compared to males in the auditory equiprobable Go-NoGo task. This was caused mainly by larger Go-P3 amplitudes in females. No difference in NoGo-P3 amplitudes between sexes was observed.
- N2 amplitudes did not differ between sexes in response to the auditory equiprobable Go-NoGo task.
- Longer latencies of N2 and P3 were found in females than males during auditory equiprobable Go-NoGo task.
- Systematic review provided support for potential sex-related differences; however, results are inconclusive: higher P3 amplitudes in females reported in half of the included studies, the other half found no sex effect.
- Systematic review showed that P3 latencies are mainly comparable between sexes.

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