UNIVERZA NA PRIMORSKEM
FAKULTETA ZA MATEMATIKO, NARAVOSLOVJE IN
INFORMACIJSKE TEHNOLOGIJE

ZAKLJUČNA NALOGA
(FINAL PROJECT PAPER)

PRIČAKUJ NEPRIČAKOVANO: Senzorično procesiranje v pričakovanju predvidljivih in nepredvidljivih groženj (EXPECT THE UNEXPECTED: Sensory Processing in the Anticipation of Predictable and Unpredictable Threats)

EVA KODERMAN

2018

ZAKLJUČNA NALOGA (FINAL PAPER PROJECT)

KODERMAN

UNIVERZA NA PRIMORSKEM
FAKULTETA ZA MATEMATIKO, NARAVOSLOVJE IN INFORMACIJSKE TEHNOLOGIJE

Zaključna naloga
(Final project paper)

PRIČAKUJ NEPRIČAKOVANO: senzorično procesiranje v pričakovanju predvidljivih in nepredvidljivih groženj

(EXPECT THE UNEXPECTED: Sensory Processing in Anticipation of Predictable and Unpredictable Threats)

Ime in priimek: Eva Koderman
Študijski program: Biopsihologija
Mentor: prof. dr. Gorazd Drevenšek
Somentor: prof. dr. Matthias J. Wieser

Koper, september 2018

Ključna dokumentacijska informacija

Ime in PRIIMEK: Eva KODERMAN

Naslov zaključne naloge: PRIČAKUJ NEPRIČAKOVANO: senzorično procesiranje v pričakovanju predvidljivih in nepredvedljivih groženj

Kraj: Koper

Leto: 2018

Število listov: 47 Število slik: 19 Število tabel: 7

Število prilog: 4 Št. strani prilog: 5

Število referenc: 79

Mentor: prof. dr. Gorazd Drevenšek

Somentor: prof. dr. Matthias J. Wieser

Ključne besede: senzorično procesiranje, anksioznost, nepredvidljive grožnje, EEG, N1

Izvleček:

Za anksioznost je značilno daljše stanje povečane pozornosti zaradi negotove nevarnosti (hipervigilanca). Predvidljivost je pomembna značilnost grožnje, ki vpliva na pozornost in senzorično obdelavo med pričakovanjem grožnje. Raziskave na tem področju se osredotočajo predvsem na elektrošoke, neprijetne slike in zvoke, vendar doslej še ni dobro raziskano, kako omenjene senzorične modalitete medsebojno interagirajo v stanju hipervigilance. V tej študiji smo izkoristili odlično časovno ločljivost, ki jo ponujajo dogodkovni potenciali (ERPs), da bi raziskali vpliv predvidljivosti grožnje na senzorično obdelavo in pozornosti s poudarkom na zgodnji perceptualni dejavnosti. Imeli smo 28 udeležencev, pri katerih smo se osredotočili na hipervigilanco (komponenta N1) v pričakovanju elektrošokov, neprijetnih slik in neprijetnih zvokov v situacijah brez grožnje (N), s predvidljivo (P) in nepredvidljivo (U) grožnjo. Udeleženci so ocenili neprijetnost in intenzivnost dražljajev pred in po raziskavi, s čimer smo nadzirali potencialno prisotnost habituacije. Udeleženci so rešili dva vprašalnika (State-Trait Anxiety Inventory in Beck Depression Inventory), s čimer smo preverili morebitno povezavo med procesi pozornosti in možnimi simptomi depresije in tesnobe. Hipervigilanco smo opazili le v nepredvidljivi situaciji grožnje šoka – komponenta N1 je bila povečana pri nevtralnih somatosenzornih dražljajih v nepredvidljivi situaciji z grožnjo elektrošoka. Habituacija je bila opažena zgolj pri vizualnih dražljajih. Dognanja naše študije so, da nepredvidljivost poveča pozornost, usmerjeno proti nevtralnim somatosenzornim dražljajem, če je grožnja enake modalitete. Na podlagi tega lahko trdimo, da smo opazili senzorično specifične, intramodalne procese, ki nakazujejo možgansko aktivnost, ki je senzorno pogojena.

Key words documentation

Name and SURNAME: Eva KODERMAN

Title of the final project paper: EXPECT THE UNEXPECTED: Sensory Processing of Neutral and Aversive Stimuli in the Anticipation of Predictable and Unpredictable threats

Place: Koper
Year: 2018
Number of pages: 47 Number of figures: 19 Number of tables: 7
Number of appendix: 4 Number of appendix pages: 5
Number of references: 79
Mentor: Prof. Gorazd Drevenšek, PhD
Co-Mentor: Prof. Matthias J. Wieser, PhD
Keywords: Sensory processing, anxiety, unpredictable threats, EEG, N1

Abstract:

Anxiety is characterized by a sustained state of heightened vigilance due to uncertain danger, producing increased attention to a perceived threat in one's environment. Predictability of threat impacts attentional engagement and sensory processing. Supporting research has primarily focused on shocks, unpleasant pictures and sounds, but there haven't been many studies on a combination of these three different types of threat, which is why it remains unclear how different sensory modalities interact between each other in a hypervigilant state. This study exploited the temporal resolution afforded by event-related potentials to investigate the impact of predictability of threat on sensory processing and vigilance, indexed by early perceptual activity. We recruited 28 participants and utilized a within-subject design to examine hypervigilance (N1 component) in anticipation of shock, unpleasant picture and unpleasant sound during a no (N), predictable (P), and unpredictable (U) threat task. We investigated if any habituation to stimuli was present by asking the participants to rate unpleasantness and intensity of the stimuli before and after the experiment. They completed the Beck Depression Inventory and the State-Trait Anxiety Inventory so we could see if there was any correlation between attentional engagement and possible symptoms of depression and anxiety. We observed hypervigilance only in the unpredictable threat of shock condition. N1 was enhanced for the neutral somatosensory stimuli in the unpredictable threat of shock condition.

Habituation was observed only for the visual stimuli. The present study suggests that unpredictability enhances attentional engagement with neutral somatosensory stimuli when the threat is of the same modality. This would mean that we observed sensory-specific, intramodal processes, suggesting a sensory-dependent activity.

ACKNOWLEDGEMENTS

First and foremost, I have to thank my mentor, Matthias J. Wieser of the Erasmus School of Social and Behavioural Sciences at the Erasmus University of Rotterdam, without whom this thesis would have, without a doubt, been inconceivable. I am extremely thankful and indebted to him for sharing expertise, and sincere and valuable guidance and encouragement extended to me. His diligent assistance and dedicated involvement in every step throughout the process made it very informative, interesting, and fun. Thank you very much for giving me this opportunity.

I would also like to thank my mentor Gorazd Drevenšek. He consistently allowed this paper to be my own work, but steered me in the right the direction whenever he thought I needed it. Thank you for all your valuable comments.

I must express my very profound gratitude to my parents for providing me with support and continuous encouragement through the process of researching and writing this thesis. Hvala za vse!

I would also like to thank Blaž for all the moments when my motivation was low. You and Finn mean the world to me. Thank you for reminding me to ‘keep it real’!

Finally, I also place on record my sense of gratitude to all who have directly or indirectly, lent their hand in this venture—our international co-ordinator Aleš Oven, my colleagues at the Erasmus University of Rotterdam, and Wolfert.

TABLE OF CONTENTS

LIST OF TABLES

TABLE OF FIGURES AND CHARTS

APPENDIX

APPENDIX A
CONSENT FOR PARTICIPATION IN THE EXPERIMENT

APPENDIX B
CUE VERIFICATION TEST

APPENDIX C
PAIN - THRESHOLDING PROCEDURE

APPENDIX D
CONDITION DESCRIPTION WITH FIGURES

LIST OF ABBREVIATIONS

ANOVA — Analysis of variance
BDI — Beck Depression Inventory
CMS — Common mode sense
DMN — Default mode network
EEG — Electroencephalography
ERP — Event-related potential
fMRI — Functional magnetic resonance imaging
HPA — Hypothalamus-pituitary-adrenal axis
MPFC — Medial prefrontal cortex
NPU — No threat, predictable threat, and unpredictable threat
PCC — Precuneus/posterior cingulate cortex
SAM — Sympathetic adrenomedullar system
SD — Standard deviation
STAI — State-trait Anxiety Inventory

1 INTRODUCTION

In recent years we have witnessed a proliferation of studies focusing on sensory processing of threats in hope to better understand the underlying mechanisms of anxiety when an individual goes into a state of hypervigilance. It is still unclear how the information in this state is processed, specifically how different sensory modalities interact among themselves. Unwanted possibilites or threats from the environment can turn out to be predictable or unpredictable and how we react to them can be critical for our survival. Unpredictable threats induce sustained anxiety, followed by vigilance, whereas imminent, predictble threat leads to phasic fear with selective attention (Grillon, Baas, Lissek, Smith and Milstein, 2004). Recent research suggests that threatening context can sensitize reactivity to stimuli in all sensory modalities (Baas, Milstein, Donlevy and Grillon, 2006; Cornwell et al., 2007; Dunning, DelDonno and Hajcak, 2013; Sharvit, Vuilleumier, Delplanque and Corradi-Dell’Acqua, 2016), however it remains unclear whether these neural mechanisms occur across different sensory modalities crossmodally, supramodally or intramodally (Cecchetti, Kupers, Ptito, Pietrini and Ricciardi, 2016; Dieterich, Endrass, and Kathmann, 2016; Domínguez-Borràs, Rieger, Corradi-Dell’Acqua, Neveu and Vuilleumier, 2017; Driver and Noesselt, 2008). This study will therefore focus on how exactly anxiety alters sensory information processing in three distinct sensory modalities while anticipating predictable and unpredictable threats.

By broadening our knowledge on how anticipating different types of threats with our senses occurs in a healthy population, we can better understand the deficits when anxiety becomes a disorder. For this reason, the present study was done on a healthy population in hope that the results will contribute to the development of better treatment for the underlying psychopathology in anxious patients.

1.2 Anxiety

Barlow (2000) described anxiety as a coherent cognitive-affective structure with its core in a sense of uncontrollability focused on possible future threats, danger, or other upcoming potentially negative events. Unpredictable threat leads to generalized apprehension and hypervigilance (indicating readiness and preparation to deal with a potentially aversive event), whereas predictable threat elicits a “fight or flight” response that is produced by an identifiable threat. Grupe and Nitschke (2013) defined hypervigilance as a state of increased attention to a perceived threat in one's environment. Anxiety is tightly tied to hypervigilance, as it plays a critical role in maintaining it. It is supposed that threat-related arousal facilitates greater attention to a threat and decreases cognitions that would inhibit anxiety (Kimble et al., 2013).

Attention is the process by which the information that we find personally salient reaches our awareness and directs action (Todd and Manaligod, 2017). It is the ability to restrict neural processing only to a relevant subset of stimuli while simultaneously excluding task-eligible stimuli from consideration. This usually takes place in the cerebral neocortex (Krauzlis, Bogadhi, Herman and Bollimunta, 2018). Petersen and Posner (1990) suggested that the attention system is anatomically separate from processing systems and that it handles incoming stimuli, makes decisions, and produces outputs. It is combined of a network of anatomical areas which carry out different specific functions. The alerting network is focused on brain stem arousal systems along with the right hemisphere systems that are related to sustained vigilance. The second network is an orienting network, which prioritizes sensory input by selecting a modality or location, and the third an executive network, the process of target detection. Anxiety shifts the attention away from a task-directed mechanism to a sensory-vigilance network, that is governed by the amygdala rather than the prefrontal cortex (Bishop, 2007; Bzdok, Laird, Zilles, Fox and Eickhoff, 2012). The amygdala is a part of the limbic system, a broad area of the forebrain located between the neocortex and hypothalamus that coordinates behavioural and physiological responses to threat—its subcomponents are responsible for processing and integrating environmental information, social information processing, and mounting appropriate attentional, vegetative, and motor responses (Bzdok et al., 2012). It is a highly conserved brain structure that is fundamental to detecting potential danger (Janak and Tye, 2015). Hyperactivation of the amygdala can lead to symptoms of depression and anxiety (Swartz, Knodt, Radtke and Hariri, 2015; Yang et al., 2008). On the other hand, the prefrontal cortex receives information about all sensory modalities and about the motivational and emotional state of the individual, and can be termed as the brain's “executive” (Miller and Wallis, 2013; Niedermeyer, 1998). It provides associations between cues and potential threats (Milad and Quirk, 2012). Damage done to the prefrontal cortex can cause difficulties in sustaining attention, keeping "on task", and leads to irrational and impulsive behaviour (Miller and Wallis, 2013).

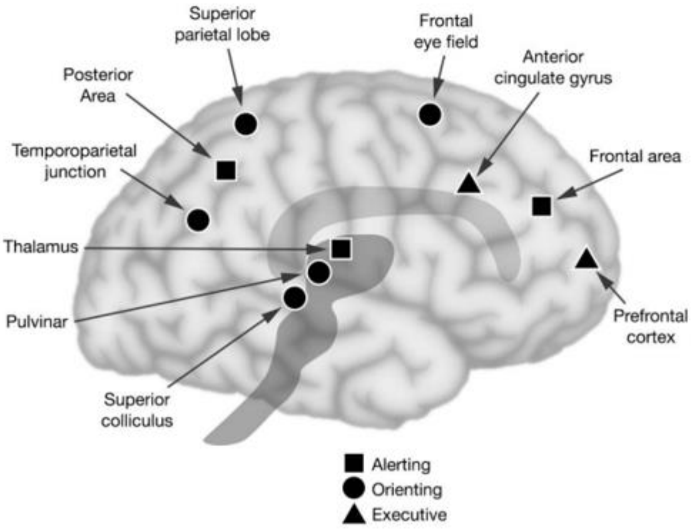


Figure 1.01. Anatomy of three attentional networks—the alerting, orienting and executive attention (adapted from Posner and Rothbarth, 2007).

1.2.1 Anxiety and Sensory Processing

Touch, smell, taste, sight, and hearing are separate physiological channels that provide us with different maps of the world. However, we do not experience the world through a single modality—by contrast, real-world situations often stimulate several of our senses concurrently, as an incoming stimulation across different modalities. For example, we see the person we are talking to, hear what they are saying, and, if touching, feel them all at the same time (Rouby, Fournel and Bensafi, 2016). The signals of different sensory modalities are processed in anatomically distinct brain areas, and the underlying mechanisms allow them to interact in order to build reliable representations of our environment and to guide our behaviour accordingly (Macaluso, 2006). A key characteristic of the brain is to segregate and integrate the processed information through anatomical and functional connections between brain regions. Functional interactions are provided by synchronized activity, both locally and between distant brain regions (Lang et al., 2012).

With the development of noninvasive brain imaging techniques, such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), more accurate mapping of brain functions has been made possible. Several sensory-specific areas were identified, responding to stimuli in one or another sensory modality. The occipital cortex was localized for vision, the superior temporal gyrus for audition, and the postcentral regions for touch, which can be seen in Figure 1.02. However, it has been established that signals in different modalities can interact with one another, giving rise to multisensory integration, the study of how information from different sensory modalities can be integrated by the nervous system. Multisensory interactions can affect how we direct attention in space, such as improving our judgment of a visual stimulus by pairing it with a tactile or auditory stimulus (Macaluso, 2006). It has been shown to enhance and speed up detection, localization, and reaction to biologically and emotionally significant events (Stein, Stanford and Rowland, 2009). Neuroscience has identified multiple "multisensory" brain regions as convergence zones. In those regions neurons receive afferent inputs from several senses and combine them. This multisensory interplay that involves interactions between various sensory modalities can be termed as crossmodality, whereas sensory-specific processes, implying a single unified percept, can be termed as intramodality (Driver and Noesselt, 2008).

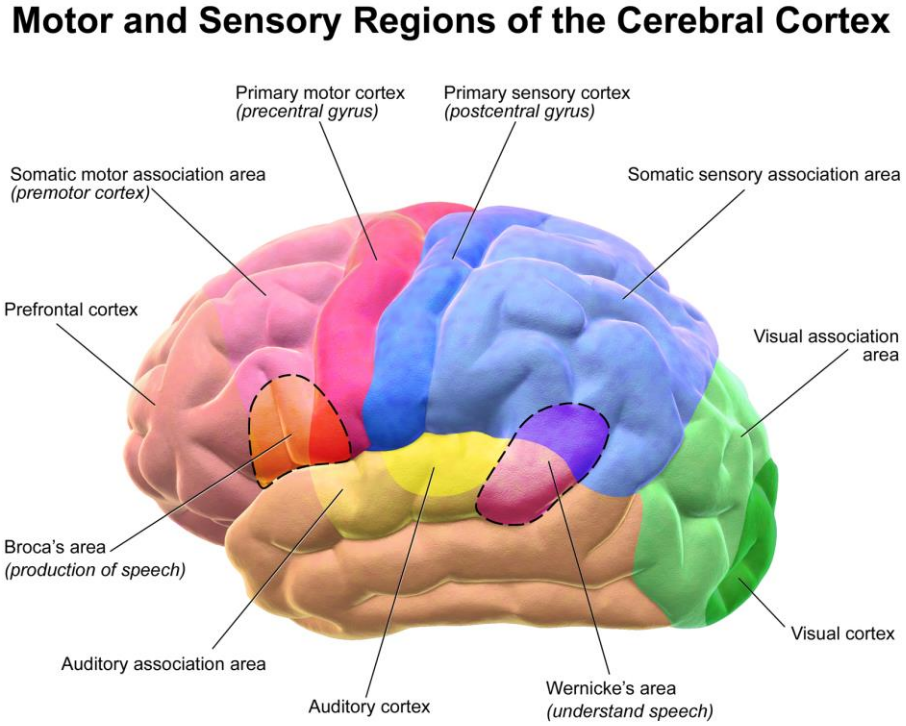


Figure 1.02. Motor and sensory regions of the cerebral cortex (adapted from Blausen, 2014).

Recently, the increasingly extensive search for multisensory processes has led to the surprising discovery that regions traditionally considered as purely sensory-specific can also show multisensory effects (Macaluso, 2006). Temporal, spatial, and task-related constraints can determine whether sensory-specific cortices engage in multisensory processing. This raises the question of how information of one modality can reach brain regions dedicated to a different modality. There are two main hypotheses that could provide an answer. One involves top-down influences from multisensory regions onto sensory-specific areas, while the other considers direct anatomical connections between sensory-specific areas (Macaluso, 2006). However, the brain areas can also respond to specific information independently of the modality conveying the sensory input. This is a supramodal thesis, however some authors refer to it as a “task-specific sensory-independent” activity (Heimler, Striem-Amit and Amedi, 2015), since these supramodal responses do not depend on a specific sensory modality (Cecchetti et al., 2016). An example of a supramodal network are the areas of the brain that process language and integrate visual, auditory, and tactile areas (Lindenberg and Scheef, 2007).

It is important to note that authors have been investigating the question of whether stimulus representations from different modalities compete with one another for neural resources. Such competition among modalities would mean that there is evidence of shared crossmodal resources, whereas the lack of competition would point to independent, modality-specific attentional processing (Rapp and Hendel, 2003). Research to date indicates that the attentional system can, in fact, be internally organized both into distinct modality-specific and crossmodal mechanisms of attention (Rapp and Hendel, 2003). Domínguez-Borràs and colleagues (2017) wished to establish whether it is the emotionally significant stimuli that enhance attention and perception when stimuli are simultaneously presented across different sensory modalities. The results showed that emotional modulation heightened sensory reactivity for somatosensory and auditory modality, with no apparent cost to sensory competition. However, visual responses showed a decrease, indicating a mechanism of sensory competition within the visual modality caused by the emotionally significant visual stimulus. This study confirmed and expanded the crossmodal model of attention, which considers that attentional mechanism modulates early modality-specific neural responses across the visual, auditory, and somatosensory cortices, indicating that these effects are controlled by supramodal networks for emotional regulation of perception and attention (networks for sensory response potentiation and sensory response inhibition).

1.3 Threats

1.3.1 Threats and Behavioural Responses

When the individual is presented with a completely new stimulus, a dilemma is presented—should the stimulus be avoided or approached? If such stimuli are perceptually similar to those associated with danger in the past, they can be evaluated by the individual as potential threats, and the organism responds with defensive responses, such as avoidance or immobility (Grosso, Santoni, Manassero, Renna and Sacchetti, 2018). The stress system, the response to and trigger of stressful stimuli, integrates a wide diversity of brain structures which enable us to detect events and interpret them as either real or potential threats, termed stressors (Dedovic, Duchesne, Andrews, Engert and Pruessner, 2009). This perception of real or potential threats leads to interaction between mediating molecules with their corresponding receptors in the periphery as well as in the brain and results in the stress response, which restores the body homeostasis and promotes adaptation (Joëls and Baram, 2009; de Kloet, Joëls and Holsboer, 2005). Identification of a stressor, either physical or psychological, leads to the activation of two major constituents of the stress system, the first being the sympathetic-adreno-medullar axis, which secretes noradrenaline and norepinephrine, and the second the hypothalamus-pituitary-adrenal (HPA) axis, which secretes glucocorticoids. Once these axes are activated in response to a given threat, they will coordinate a response enabling both an appropriated strategy to deal with threats almost immediately and a homeostasis restoration. To accomplish this, the stress response involves energy mobilization, metabolic changes, activation of the immune system, and suppression of the digestive and reproductive systems. Specifically, the short- and long-term effects in the brain include non-genomic, genomic and epigenetic mechanisms, which, combined with proinflammatory signalling, lead to alterations in cellular excitability as well as synaptic and neuronal plasticity. All of these effects in the body and the brain mediate alterations in physiology and behaviour that enable adaptation and survival (Godoy, Rossignoli, Delfino-Pereira, Garcia-Cairasco and de Lima Umeoka, 2018).

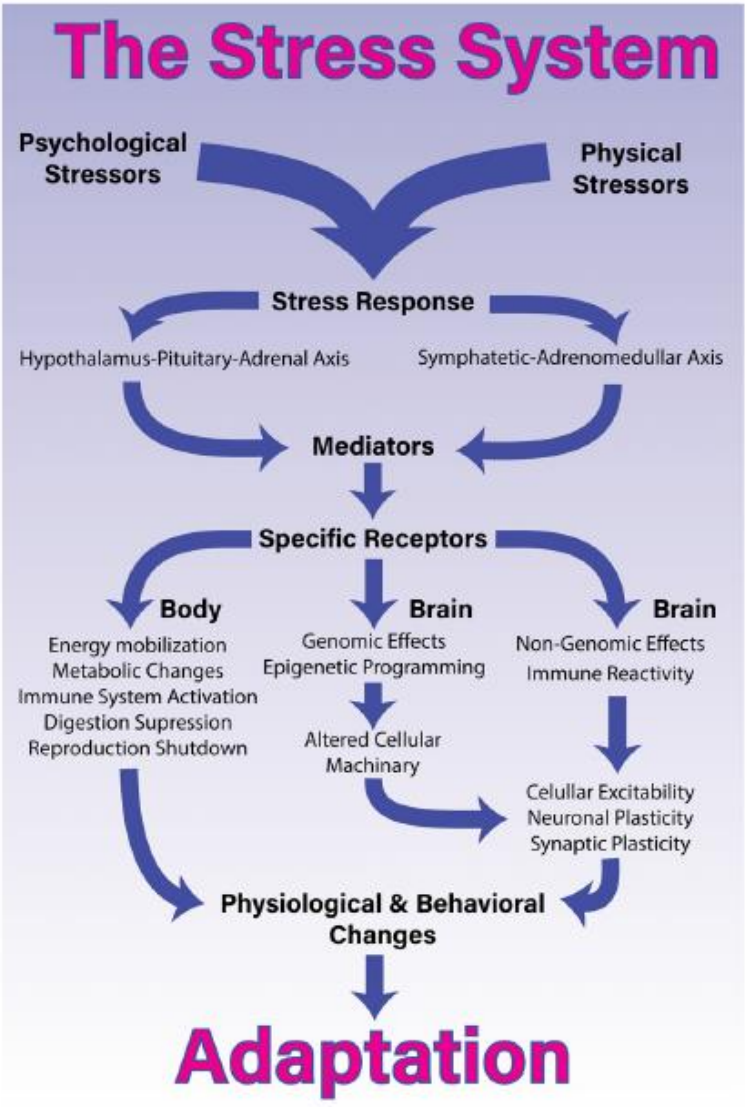


Figure 1.03. The stress system (adapted from Godoy et al., 2018).

The first phase of the response to a potential threat (sympathetic adrenomedullar system—SAM) provides a rapid physiological adaptation resulting in short-lasting responses, such as alertness, vigilance, and appraisal of the situation, and enables the individual to deal with the threat in the initial phase (Joëls and Baram, 2009; de Kloet et al., 2005).

When the stress system is not able to overcome the environmental, physiological, or emotional demand, it can become disrupted. This occurs when the demand is extremely strong or chronic and/or during development (Godoy et al., 2018). Chronic stressors in early life can result in permanent epigenetic, endocrine, neural, immune, and inflammatory changes, constituting a relevant risk factor for several neuropsychiatric diseases in adult life (Berens, Jensen and Nelson, 2017; Xiong and Zhang, 2013). Anxiety disorders tend to be more common in people who experience stress early in life (Fernandes and Osório, 2015)

1.3.2 Unpredictable and predictable threats in anxiety

Prediction plays a crucial role in the quality of our life. It allows us to have representations of a particular future event upon which we can produce future-oriented actions, decisions, or behaviours, a network that can be termed anticipation (Pezzulo, 2008). In this section I will present current research on the underlying anticipatory attentional mechanism and how neural mechanisms differ with regard to whether we can accurately predict threat in our environment or not.

According to Bidet-Caulet et al. (2012) extraction of informative cues from the surrounding environment occurs through a preparatory mechanism via the deployment of several anticipatory mechanisms—anticipation of imminent threats facilitates the processing of the incoming stimulus, improving the selection and execution of the behavioural response. However, depending on what is expected, different preparation mechanisms are involved. Enhanced excitability in visual cortices was observed as a result of the attentional preparation mechanism before the stimulus onset, which induced quicker target detection and processing. Yet when participants expected a target requiring a motor response, the motor preparation mechanism was activated by enhancing excitability in the motor cortices before movement onset.

Neural mechanism are quite different when we don't know what to expect. Dieterich et al. (2016)) examined how attention is allocated under uncertainty about a potential threat. They found expectancy and covariation biases—participants overestimated the frequency of aversive stimuli under uncertainty, while showing a tendency for more negative subjective valences in response to aversive stimuli following uncertain cues. One of the key findings is that uncertainty-induced increase in early attention cannot be modulated by selective processing of neutral and aversive stimuli. This was not specific to visual stimulus processing, which would suggest a generally enhanced attentional response to uncertainly cued targets. These underlying attentional mechanisms produce an ongoing screening for threat in the environment and a continuous elaboration of neutral stimuli which deviate from expectation, indicating the presence of sustained attention for uncertainly cued targets.

1.4 NPU-threat task

Schmitz and Grillon (2012) established a procedure termed the NPU-threat task, in which fear and anxiety are examined in a laboratory environment. The N stands for no threat condition, where participants are completely safe from threat; P stands for predictable threat, where the threat is signalled by a threat cue; and U for unpredictable threat condition, in which aversive stimulus can happen at any time. During the NPU-threat task, a change in aversive states is usually measured by the startle reflex as an indicator of defence system activation. Multiple studies using the NPU-task have found that the startle reflex is potentiated in anticipation of predictable and unpredictable threat in comparison to no threat (Dieterich et al., 2016; Domínguez-Borràs et al., 2017; Grillon et al., 2004; Nelson and Hajcak, 2017; Nelson, Hajcak and Shankman, 2015) and that startle potentiation is greater for unpredictable threat in comparison to predictable threat (Gorka, Lieberman, Shankman and Phan, 2017; Nelson et al., 2015).

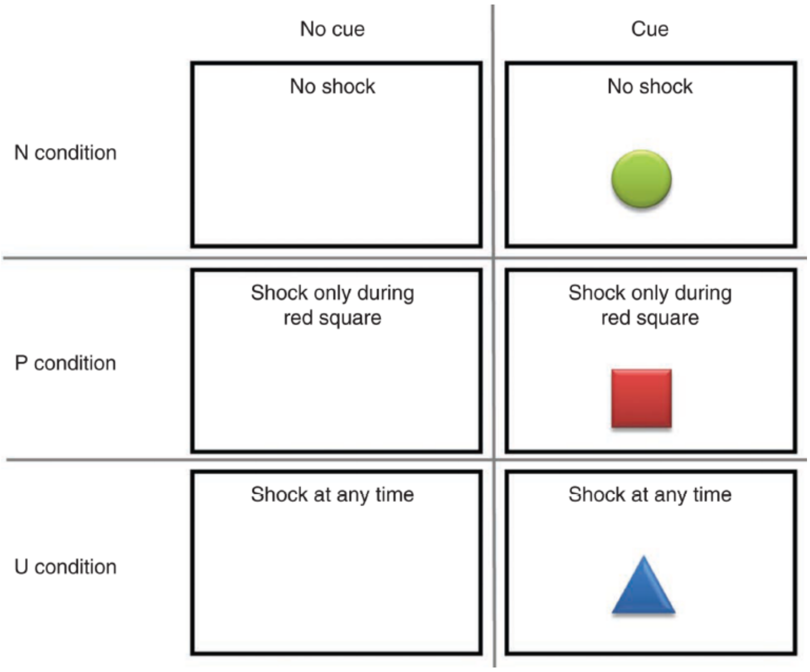


Figure 1.04. Visual material presented during the experiment by cue/no cue status and condition (adapted from Schmitz & Grillon, 2012).

1.5 Event-Related potentials

Event-related Potentials (ERPs) are derived from the continuous EEG by averaging the brain responses to repeated presentations (events) of stimuli. They are especially useful for examining rapid processing of potentially threatening stimuli (LeDoux, 2000). To further investigate the impact of threat on attention, the current study measured ERP responses elicited by non-painful electrical stimulation, pictures, and sounds during the NPU-threat task. The event-related potential (ERP) is a technique that has proven to be particularly effective for testing theories of perception and attention due to its precise temporal resolution of electrophysiological recordings. Instead of recording a summation of the action potentials generated by individual neurons, the EEG and averaged ERPs measure electrical potentials that are generated in the extracellular fluid in the form of ions flowing across cell membranes as neurotransmitters are transmitted. ERPs are primarily generated by the postsynaptic potentials of cortical pyramidal cells and that is why the potentials of simultaneously active neurons that have approximately the same orientation can summate (Woodman, 2010). There are some difficulties in determining the source configuration from scalp topography. A given scalp topography may have infinite numbers of course configurations. This is formally known as the “inverse problem”. There are also some “inverse solutions” that one can use to localize cortical activity (Slotnick, 2004).

We can use the ERP waveform to visualize cognitive operations as they unfold during a trial. We can do this by observing the peaks and troughs of a stimulus-locked ERP. This leads us to ERP components, which can be defined by their polarity (positive or negative voltage), timing, scalp distribution, and sensitivity to task manipulations. A specific component can refer to the underlying cognitive processes and brain activity indexed by the potential (Woodman, 2010).

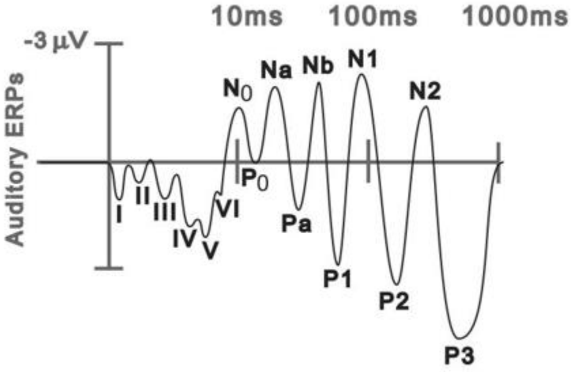


Figure 1.05. Idealized ERP evoked by a brief auditory stimulus. Waveforms shown would be expected from a central electrode site (adapted from Woodman, 2010).

Table 1.01
Summary of ERP components during a simple visual-manual task (adapted from Woodman, 2010)

Nomenclature	**Ordinal**	**Latency (peak)**	**Scalp distribution**	**Task/Stimulus specificity**	**Hypothesized Process(es) Indexed**
Components preceding a stimulus				CNV (O- & E-waves)	Anticipation, Cognitive & Motor preparation
	C1	P/N50-70			Sensory processing
	P1	P90-100			Sensory/Perceptual processing
	N1	N170-200	Posterior versus Anterior	N170 for faces	Perceptual processing, Expert recognition, Visual discrimination
	P2				Not well understood
Components following a stimulus	N2	N225-250			Object recognition, categorization
	N2pc		PCN		Deployment of covert attention
	P3	P300	P3a/P3b	P3a/P3b	Stimulus evaluation time, categorization, context (working memory) updating, cognitive load
			SPCN	CDA	Maintenance in visual working memory
				LRP	Response preparation

Notes: CNV, Contingent Negative Variation; O- & E-waves, Orienting & Expectancy Waves; C1, component 1; N, negative; P, positive; N2pc, N2-posterior-contralateral; PCN, Posterior Contralateral Negativity; CDA, contralateral-delay activity; SPCN, Sustained Posterior Contralateral Negativity; LRP, Lateralized Readiness Potential

The N1 is a negative deflection in the ERP waveform that peaks approximately 80–100 ms after the onset of the stimulus at frontocentral electrodes and indicates early perceptual processing of stimuli. It is enhanced when looking at unpleasant in comparison to pleasant and neutral pictures (Cuthbert, Schupp, Bradley, Birbaumer and Lang, 2000 The enhancement as a result of incoming information is an indicator of increased early vigilance and augmented sensory intake for somatosensory threats (Shackman, Maxwell, McMenamin, Greischar and Davidson, 2011). We therefore chose to focus on the N1 as an early indicator of attentional processing in the anticipation and predictability of threat in different sensory modalities and with it explore common neural mechanisms across senses.

Nelson et al. (2015) examined early activation of our defence system in anticipation of no, predictable, and unpredictable shock by observing the P3 and N1 components. Their findings show that the N1 was enhanced at frontocentral sites in anticipation of unpredictable shock and indicate that the increased N1 may serve as an important component in attention that primes early processing of sensory input when we anticipate possible (unpredictable) danger in our environment. P3 was attenuated, indicating that anticipation of threat in general engages later attention processing. It was one of the first studies done to use startle probe ERPs to demonstrate how the context of a potential threat elicits attentional engagement. They used the NPU-threat task, but included only one modality—the somatosensory.

In a later study Nelson & Hajcak (2017) examined attention in anticipation of threats in two different types of sensory processing—visual and somatosensory. They found that the startle reflex and the participant's ratings of their own feelings on a scale from 1 (not at all anxious) to 7 (extremely anxious) after each condition were greater in anticipation of both types of threat in comparison to no threat, which was further augmented for unpredictable compared to predictable threat. The N1 was, again, enhanced in anticipation of unpredictable threat in comparison to predictable and no threat in both shock and unpleasant picture trials, meaning that unpredictability enhanced attentional engagement in anticipation of threat in both modalities. However, the shocks elicited greater defensive motivation than unpleasant pictures, which indicates that more intense aversive stimuli are associated with increased effects of unpredictability on the startle reflex. Concerning the neural indicator of the attentional allocation (N1), one of the key findings was that when we compare shocks and unpleasant pictures, the type of threat does not play such an important role as does the potential for threat in general. It is important to note that this study was one of the first to use unpleasant pictures in the NPU-threat task.

Threat-elicited stress is also an important factor that governs our organism's response in a situation when threat is encountered. In an older study Shackman and colleagues (2011) observed early N1 component amplification in participants that were at random exposed to shocks while performing a simple task. This amplification indicates that threat-related stress (shocks at random) altered attention by amplifying early sensory processing of non-threatening stimuli due to vigilance for threat. At the same time, the later activity of P3 component was attenuated, indicating disrupted task-directed processing. This supports the notion that in anxious anticipation of an uncertain threat, our organism shifts the attention from the prefrontal cortex to the amygdala (Bishop, 2007; Bzdok et al., 2012; Posner and Petersen, 1989).

In general, larger N1 amplitudes that occur in response to nonthreatening stimuli have been found in populations prone to high levels of anxiety, such as panic attacks (Wise, McFarlane, Clark, & Battersby, 2009), social anxiety (Felmingham, Stewart, Kemp, & Carr, 2016), and PTSD (Zukerman et al., 2018). The N1 was specifically enhanced in those with PTSD in a study done by Zukerman et al. (2018) when participants were presented with the auditory novelty oddball paradigm to discriminate between target, novel, and standard tone. Such findings are especially indicative of hypervigilance of early automatic attention.

1.6 The aim of our study and research questions

The goal of our study was to investigate sensory processing during anticipation of predictable and unpredictable threats in three different modalities (auditory, visual, and tactile). Specifically, the emphasis was on the neutral stimuli presented after the cue and just before the threat to capture the neural mechanisms of anticipation. We wished to examine if the state of hypervigilance alters the attention to neutral stimuli in any of the three modalities. In addition, we wanted to establish if sensory processing is selectively influenced during anticipation of threat. To sum up, our main research question was how anticipation of threat affects sensory responses in the auditory, visual, and somatosensory modalities.

There has been a proliferation of studies on the connection between emotionally significant stimuli and sensory processing and attention. With predictable threats, the brain mechanisms work through several anticipatory mechanisms depending on what is expected (Bidet-Caulet et al., 2012), which is different from uncertainty-induced early attention, since the latter is not selectively influenced but generally enhanced to uncertainly cued targets. Stimulus that is presented after an uncertain cue (either neutral or aversive) tends to elicit an enhancement of early phasic and sustained attention, a neural indicator observable with the N1 component (Dieterich et al., 2016). These targets are processed through different sensory processing channels. Here, the results of previous studies have yielded inconsistent findings. Some argue that the sensory modality does not play a crucial differentiating role in the N1 enhancement, and that different types of aversive stimuli produce comparable attentional engagement (Nelson and Hajcak, 2017). Others say that due to sensory competition, the type of threat is an important factor in attentional allocation in the anticipation of unpredictable threat. Sensory effects that would be irrelevant in neutral conditions may become more salient in a threatening environment, only when these events do not compete within a sensory channel (Domínguez-Borràs et al., 2017). However, the amplification of the N1 component is an indicator of early attentional engagement (vigilance for threat) caused by the anticipation of unpredictable threat (Nelson et al., 2015; Nelson and Hajcak, 2017; Shackman et al., 2011).

A review of literature on this subject has led us to formulate the following hypotheses:

H1: When anticipating unpredictable threat, hypervigilance in all three sensory modalities can be observed as indexed by the enhancement of the N1 component.

H2: The enhancement of the N1 component in all three sensory modalities in anticipation of unpredictable aversive stimuli compared to predictable aversive stimuli or no aversive stimuli proves the presence of supramodality, suggesting a sensory-independent activity.

H3*:* The enhancement of the N1 component for neutral stimuli of the same sensory modality as the aversive stimuli proves the presence of intramodality, suggesting a sensory-dependent activity.

2 METHODS

2.1 Participants

Subjects (7 male, 22 female) were undergraduate Psychology students at the Erasmus University of Rotterdam who obtained course credits in exchange for the participation. All participants provided written informed consent (Appendix A) and the research protocol was approved by the Ethical Comittee of Erasmus University of Rotterdam. The social demographics of the sample are presented in Table 2.01. The data of one female participant, who was feeling anxious during the experiment and decided to withdraw, was excluded. The final number of participants was 28. Exclusion criteria were psychiatric or neurological disorders (for example epilepsy). The participants were informed about the conditions that would distort the EEG data (hair gel, any kind of skin make-up …) and asked to avoid them on the day of the experiment.

Table 2.01
Social Demographics

		N	*M*	*SD*	*Min*	*Max*
Age	Female	22	20.82	2.91	18	29
	Male	6	20.83	1.60	18	23
Nationality	Dutch nationality and origin	7				
	Dutch nationality and other descent	2				
	Other nationality and origin	19				

2.2 Apparatus and measures

2.2.1 Stimuli

For the auditory neutral stimulus we used a beep tone with a fundamental frequency of 500 Hz, played at a volume of 70 dB. For auditory aversive stimulus we used the sound of a woman screaming at 90 dB. For somatosensory neutral and aversive stimulus we used electrical stimulation at individual pain threshold administered to the left lower arm muscle (M. Brachioradialis); the neutral and aversive stimulus differed in their duration as described below (see Procedure). Gabor patches were used for visual neutral stimulus. For visual aversive stimulus we selected a picture from the International Affective Pictures

System that presented a murdered man (IAPS; Lang et al. 2008). The visual stimuli and cues had a size of 500 x 500 pixels.

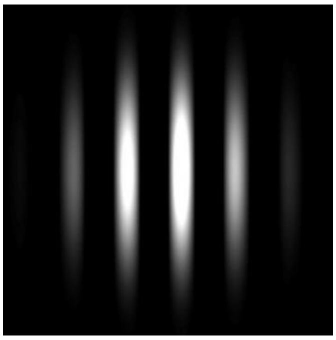


Figure 2.01. Neutral visual stimulus.

Figure 2.02. Aversive visual stimulus.

The stimuli were presented to the participants in an isolated room with a screen at a viewing distance of approximately 1 m. The screen size was 1024 x 768 pixels on a 22″ screen.

2.2.2 Questionnaires and Tests

State-Trait Anxiety Inventory (Spielberger et al., 1983) was used to measure state anxiety (current state of anxiety) and trait anxiety (anxiety on a personal level). The inventory is based on a 4-point Likert scale and consists of 40 questions on a self-report basis. 20 items are allocated to each the state or trait anxiety, respectively. Responses for state anxiety asses feelings “at the moments”: 1) not at all, 2) somewhat, 3) moderately so, and 4) very much so. The responses for trait anxiety scales asses frequency of feelings: 1) almost never, 2) sometimes, 3) often, and 4) almost always. Higher scores are positively correlated with higher levels of anxiety. Before the experiment, the participants filled out the STAI questionnaire and the Beck Depression Inventory (Beck, 1961) on a computer. The BDI measure is a 21-item scale with a good internal reliability and consistency. It also picks up anxiety states to some extent and focuses less on the somatic aspects of depression (Beck, 1961).

The anxiety scores from the STAI questionnaire (Spielberger et al., 1983) were within the normal range in all cases (STAI-State: M = 38.6 vs 38.8 in standard population, SD = 10; STAI-Trait: M = 42.4 vs 40.4 in standard population, SD = 8.2).

Table 2.02
Descriptive statistics for the BDI and the STAI results

	N	*Minimum*	*Maximum*	*Mean*	*Std. Deviation*
BDI	28	.00	20.00	7.76	5.72
State Anxiety Sum	28	20.00	57.00	38.64	10.50
Trait Anxiety Sum	28	24.00	56.00	42.43	8.24
Valid N (listwise)	28				

After the experiment, subjects estimated the probability of a threat occurring after each cue on a written test (Appendix B). The purpose was to verify whether the subjects understood the cues throughout the experiment.

2.2.4 EEG equipment

Continuous EEG was recorded using an elastic cap with 64 sintered Ag/AgCl electrodes placed according to the international 10/20 system (Oostenveld & Praamstra, 2001). An electrooculogram was recorded using four additional facial electrodes: two placed approximately 1 cm outside of the right and left eyes and two placed approximately 1 cm above and below the left eye. Data was recorded using the BioSemi ActiveTwo amplifier.

Signals were recorded with a low-pass filter of 134 Hz and were digitized with a sample rate of 512 Hz and 24-bit analog/digital conversion. BioSemi uses the common mode sense (CMS) and driven right-leg electrodes to create a feedback loop that replaces the conventional ground electrode. The CMS was used as an online reference.

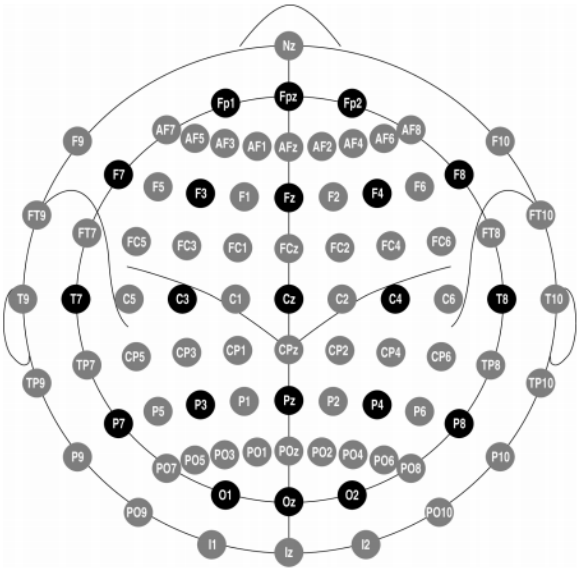


Figure 2.03. The placement of electrodes according to the 10/20 system. Black circles indicate positions of the original 10±20 system, gray circles indicate additional positions introduced in the 10±10 extension (adapted from Oostenveld and Praamstra, 2001).

2.3 Procedure

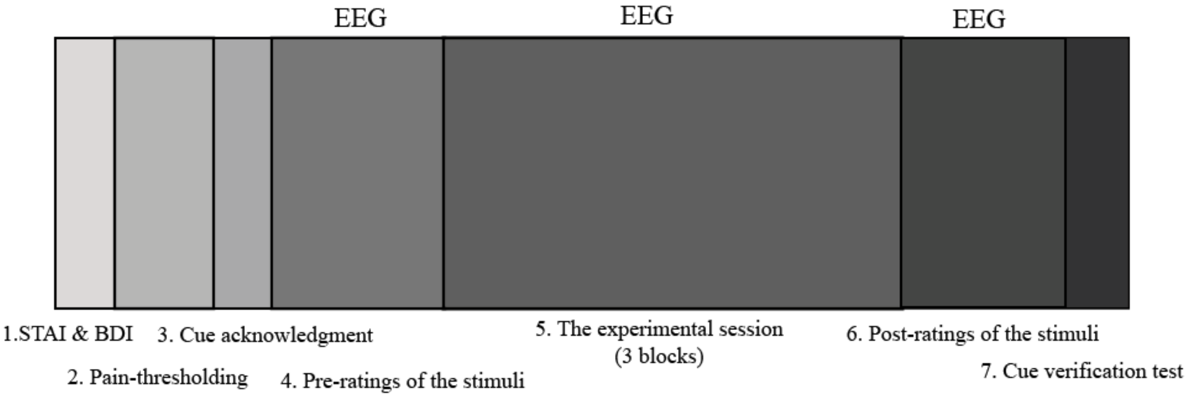


Figure 2.04. The procedure of the experiment—the length of each box presents the approximate duration of each step.

Participants first read and signed the consent form and then completed the STAI and BDI questionnaires on the computer which took approximately 10 minutes. The next phase of the experiment took place in an isolated room where the EEG recording took place. We measured the head circumference to choose the appropriate cap for each participant. The gel was applied to each electrode to enable conductivity. When the EEG was set up, we proceeded with the pain thresholding procedure which lasted for approximately 10 minutes. Each individual's pain-threshold was measured to define the intensity of the somatosensory stimuli. We used an electric stimulus with a frequency of 50 Hz generated by a constant current stimulator (Digitimer DS7A, Digitimer LTD., Welwyn Garden City, UK). Prior to the pain thresholding procedure a scale from 0 to 10 was presented to a subject, 4 indicating "just noticeable pain". Participants received increasing levels of shock, with 2 series of increases of the electrical stimulation and 2 series of decreases, starting with 0 mA (Appendix C). The direction changed each time a subject rated the shock as 4. The electrical current increased and decreased always by 1 mA. To determine the pain threshold we took the electric charges rated as 4, calculated the mean and added 30%. The electrical stimulation was always applied once for the duration of 2 ms. The mean shock intensity level across the entire sample was 2.34 mA (*SD* = 1.65) and the rating 5.72 (*SD* = 0.97).

After the pain thresholding procedure, the subjects were explicitly instructed about the predictive value of cues (Appendix D). Next, they had to rate neutral and aversive stimuli, measuring their intensity and unpleasantness. The question "How intense do you find this stimulus?" was displayed on the computer screen, after which the stimuli were presented one by one. The participants used a cursor to choose the perceived value on a digital scale. This procedure was repeated for the question "How unpleasant do you find this stimulus?". The overall range of the scale was from -50 on the left (the least intense or unpleasant) and

50 on the right (the most intense or unpleasant). They rated the stimuli before (Pre) and after (Post) the experimental session.

For the three blocks we used the NPU-threat task (Schmitz and Grillon, 2012) as described in the Introduction. We had one condition with three levels: 100% no threat, 100 % predictable threat, and unpredictable threat (50% threat, 50% no threat). Each block had a different threat modality—one with the aversive sound stimulus (woman screaming), the second with the aversive visual stimulus (murdered man) and the third with the aversive somatosensory stimulus (long electric stimulation). Blocks were presented in one of the following orders (counterbalanced): 123, 231 or 312.

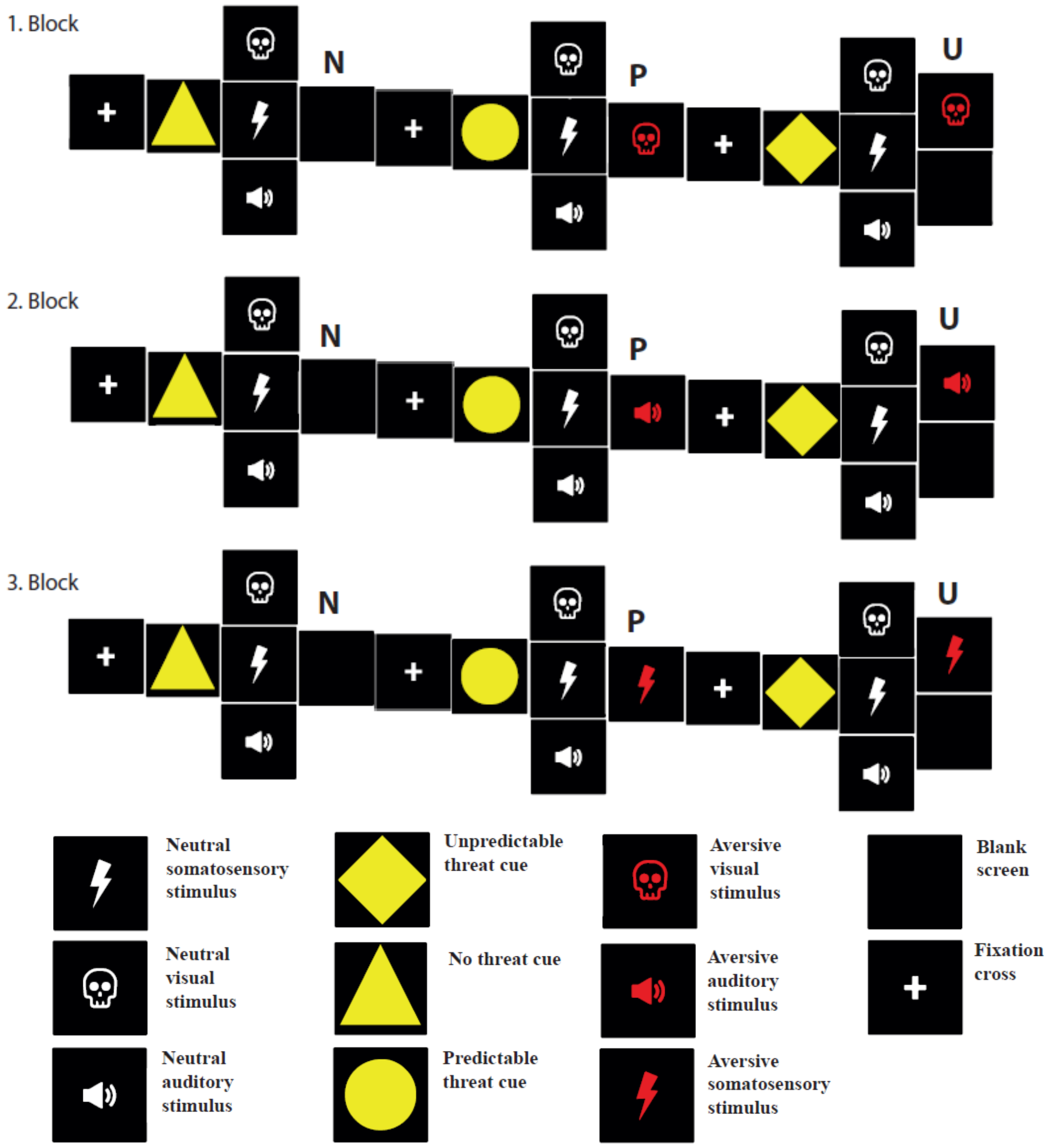


Figure 2.05. A schematic representation of an experimental trial.
Notes: N — no threat, P — predictable threat, U — unpredictable threat

Figure 2.05 is a schematic representation of an experimental trial. The triangle, circle, and diamond represent the cues, the white images represent neutral stimuli, and the red images the aversive stimuli. In the no threat condition, no aversive stimulus was presented, leaving the participant with a blank screen. In the predictable threat condition, participants received one of the aversive stimuli, depending on the block. In the unpredictable threat condition, the participants got either a blank screen (no threat) or an aversive stimulus (threat).

Each NPU condition contained 20 trials, which amounted to 540 trials in total, i.e. 180 trials per block and 60 per conditions that were randomized. A trial began with a fixation cross followed by a cue in the form of a geometric shape indicating the condition. Then the neutral stimulus was presented three times, followed by either no threat or predictable/unpredictable threat. The three blocks lasted for the duration of approximately 50 minutes.

Cues indicating the NPU condition lasted for 500 ms. The neutral visual stimulus and the neutral auditory stimulus lasted for 200 ms and were repeated for 3 times, with variable inter-stimulus intervals (1000–2000 ms). The neutral somatosensory stimulus lasted for 2 ms. The aversive visual and auditory stimuli lasted for 2000 ms and the aversive somatosensory stimulus lasted for 10 times 2 ms on and 2 ms off (40 ms). Figure 2.06 gives a visual representation of the timing of a trial.

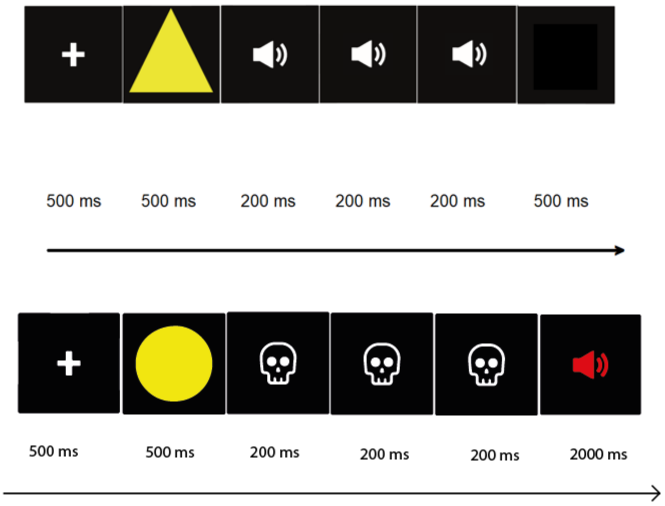


Figure 2.06. An example of the no threat trial and the predictable threat trial.

After the three blocks, participants rated the neutral and aversive stimuli in the same way as they did at the beginning. The final task of the entire experiment was a short cue verification test where participants were asked to write down the probability of a threat occurring after each cue. The whole experiment lasted for approximately 2 hours.

2.4 Data Analysis

We conducted the EEG analysis using the BrainVision Analyzer 2.1 software package (Brain Products GmbH, Munich, Germany).

Data was referenced offline to an averaged reference, band-pass filtered (0.1 to 30 Hz), and corrected for eye movement artifacts using the Gratton method (Gratton, Coles and Donchin, 1983). Data were segmented with regard to neutral stimulus onset (–200 ms onset to 400 ms). Finally, an artifact correction (exclusion of epochs exceeding > 150 mV amplitude change or low activity) and baseline correction (200 ms) was applied. The artifact rejection excludes the signals that are not the product of neuron activity in the cortex, such as artifacts coming from facial muscles, artifacts due to low conductivity between the scalp and the electrodes, and blinking artifacts.

We focused on the N1 component elicited by the neutral stimuli. For the neutral auditory stimulus we extracted the mean amplitude in the time window of 140–160 ms scored over C1, CZ, and C2. For the neutral visual stimulus we extracted the mean amplitude in the time window of 150-180 ms. For the left hemisphere we pooled the PO7, P7, and P9 and for the right hemisphere P08, P8, and P10. For the neutral somatosensory stimulus we extracted the mean amplitude in the time window of 105–135 ms, scored over Cz, C2, and C4. Since the electrode for electrical stimulation was placed on the left arm, the selected electrodes were predominantly on the right hemisphere due to contralateral processing. All electrodes were selected based on the basis of visual inspection of grand averages across all stimuli in different modalities, as seen in Figure 2.07.

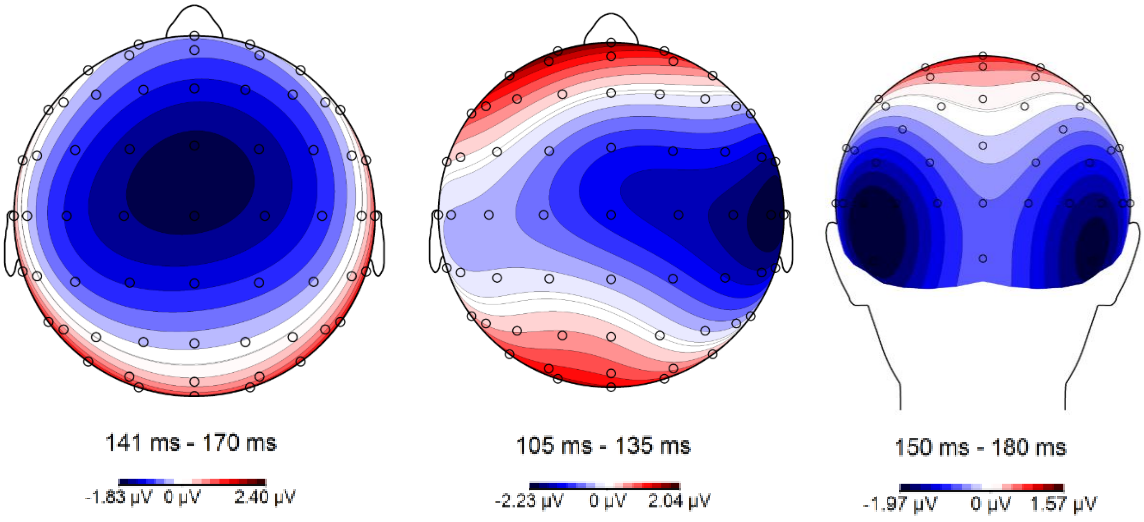


Figure 2.07. Topographic maps of the N1 activity.

The values of mean amplitudes of neutral stimuli were then exported into the IBM SPSS Statistics, version 23 (2012). Separate grand averages were conducted for each type of threat (visual, auditory, somatosensory) and each condition (no threat, predictable threat, unpredictable threat). Variables were computed including the mean of the grand averages of the three selected electrodes for each modality. Each of the new variables presented the values of mean amplitudes of electrodes from different types of threat and different conditions. For example, one of the new variables, presenting the N1 value in the somatosensory modality (extracted mean amplitudes), was the value of the overall mean average for the Cz, C2, and C4 when presented with auditory threat in the unpredictable condition. Such an approach provided 9 variables for each modality.

The N1 amplitudes were then analyzed using the repeated-measures ANOVAs including the within-subject factor 2 (*left hemisphere, right hemisphere*) x 3 (*no threat, predictable threat, unpredictable threat*) x 3 (*visual, auditory, somatosensory threat*) for the visual modality and 3 (*no threat, predictable threat, unpredictable threat*) x 3 (*visual, auditory, somatosensory*) for the auditory and somatosensory modality. Separate analyses were conducted for each modality. There were no between-subject factors. Significant interactions were followed up by post-hoc t tests with the criteria of $P < 0.05$.

The ratings of the stimuli were also exported into the IBM SPSS Statistics, version 23 (2012). The location of the cursor on the digital scale presented the value from -50 to 50. A 2 (*aversive stimuli, neutral stimuli*) x 3 (*visual, auditory, somatosensory*) and 2 (*pre-experiment, post-experiment*) x 2 (*aversive stimuli, neutral stimuli*) x 3 (*visual, auditory, somatosensory*) repeated measures ANOVAs were done on the intensity and unpleasantness ratings.

3 RESULTS

3.1 Stimuli ratings

A 2 (*neutral, aversive*) x 3 (*visual, auditory, somatosensory*) repeated measures ANOVA on the intensity $F(2,54) = 11.55$, $p < .001$ and unpleasantness ratings $F(2,54) = 14.73$, $p < .001$ yielded a significant main effect of the aversive sound stimulus, indicating it was more unpleasant and intense than the aversive somatosensory and the aversive visual stimulus. This effect is presented in Figures 3.01 and 3.02. Exact measures of the mean values of ratings can be seen in Tables 3.01 and 3.02.

Another repeated measures ANOVA 2 (*pre-experiment*, *post-experiment*) x 2 (*neutral, aversive*) x 3 (*visual, auditory, somatosensory*) on stimuli ratings yielded significant results that the aversive visual stimulus was less unpleasant after the experiment and that the aversive auditory stimulus sounded more unpleasant after the experiment $F(2,54) = 4.45$, $p = .016$. This can be seen in Figure 3.03.

Table 3.01
Descriptive statistics for the ratings of intensity of stimuli

	Mean	*Std. Deviation*
Pre shock neutral	-36.46	11.26
Post shock neutral	-38.71	11.45
Pre picture neutral	-44.36	14.53
Post picture neutral	-48.50	3.52
Pre sound neutral	-44.71	8.95
Post sound neutral	-45.75	6.46
Pre shock aversive	-7.32	20.98
Post shock aversive	-7.68	20.48
Pre picture aversive	-10.04	26.69
Post picture aversive	-14.57	30.79
Pre sound aversive	3.61	18.88
Post sound aversive	8.04	26.52

N = 28

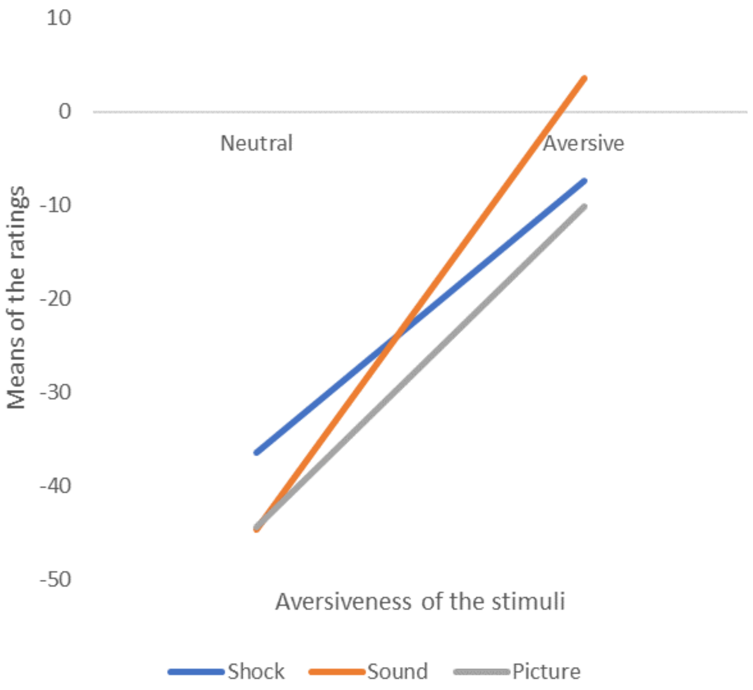


Figure 3.01. Intensity ratings for neutral and aversive stimuli in all three modalities.

Table 3.02

Descriptive Statistics for the ratings of unpleasantness

	Mean	*Std. Deviation*
Pre shock neutral	-35.43	14.91
Post shock neutral	-39.00	13.60
Pre picture neutral	-44.43	14.38
Post picture neutral	-47.71	5.97
Pre sound neutral	-46.79	5.19
Post sound neutral	-45.64	8.52
Pre shock aversive	-8.50	22.22
Post shock aversive	-7.11	23.29
Pre picture aversive	-.71	31.28
Post picture aversive	-14.00	30.71
Pre sound aversive	5.75	24.31
Post sound aversive	15.46	27.53

N = 28

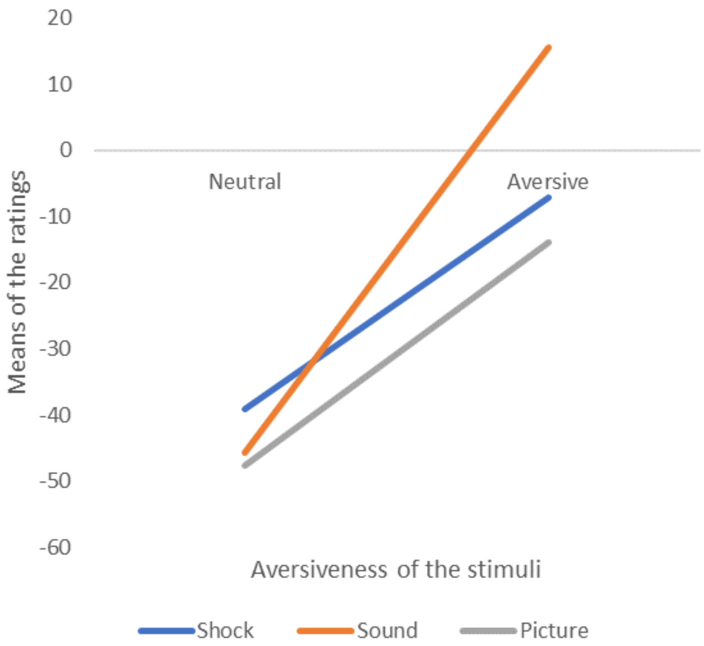


Figure 3.02. Unpleasantness ratings for neutral and aversive stimuli in all three modalities.

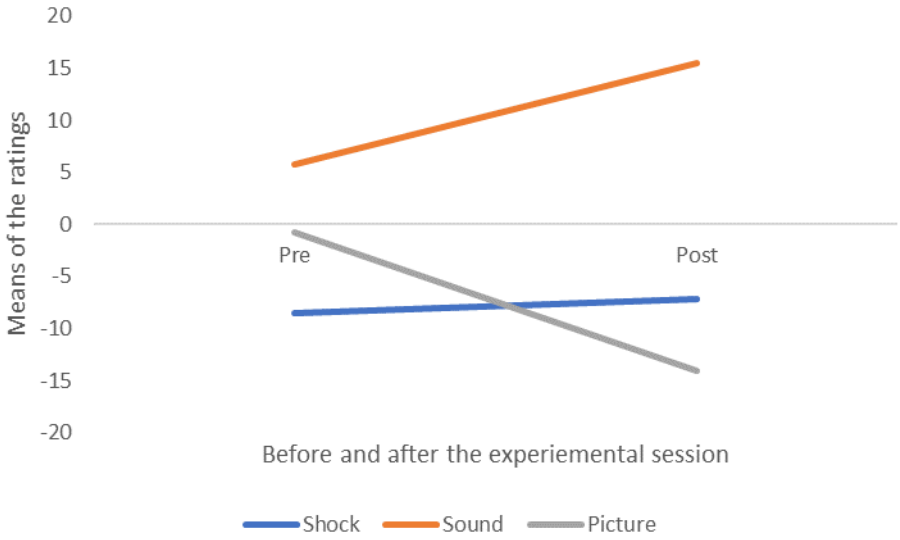


Figure 3.03. Unpleasantness ratings before and after the three blocks.

3.2 N1 amplitudes

A repeated measures ANOVA with three within-subjects factor was performed to analyze the visual modality—the two hemispheres, the three types of conditions and the three types of threats. A 2 (*left hemisphere*, *right hemisphere*) x 3 (*unpredictable*, *predictable*, *no threat*) x 3 (*auditory, visual, or somatosensory threat*) repeated measures ANOVA on the N1 amplitude yielded no significant main effect or interaction $F(4,108) = 1.52$, $p = .201$.

Another repeated measures ANOVA was performed with 2 within-subjects factors in order to analyze the auditory modality—the three types of conditions and the three types of threats. The 3 (*unpredictable, predictable, no threat*) x 3 (*auditory, visual, or somatosensory threat*) for the auditory modality repeated measures ANOVA did not yield any significant main effect or interaction $F(4,108) = 2.19$, $p = .074$. These results indicate that the N1 amplitude in the visual and auditory modality did not significantly differ between threat and neutral modality nor was there any interaction.

The 3 (*unpredictable, predictable, no threat*) x 3 (*auditory, visual, or somatosensory threat*) repeated measures ANOVA on the somatosensory modality yielded no significant main effect indicating that the N1 amplitude does not differ between the aversive and neutral modality. Nevertheless, there was significant interaction between the aversive visual stimulus and the aversive somatosensory stimulus in the unpredictable condition $F(4,108) = 2.92$, $p = .024$.

In Tabel 3.03 we can see the scores for the average of the three electrodes (Cz, C2, and C4) for the neutral somatosensory stimulus in different conditions (with no threat, predictable threat and unpredictable threat) and different threat modalities (visual, auditory, somatosensory).

Since there was significant interaction between the aversive visual and the aversive somatosensory stimulus, we performed a t-test to investigate the correlation. The correlation between the no threat condition and the unpredictable threat condition yielded significant results $t(27) = 2.39$, p .024, as did the correlation between the no threat condition and the predictable threat $t(27) = 2.47$, p .02.

Table 3.03
Descriptive statistics for the N1 component

	Mean	*Std. Deviation*
Ns	-1.58	2.16
Na	-1.37	1.80
Nv	-.87	2.21
Ps	-1.61	1.84
Pa	-1.05	1.58
Pv	-.95	1.53
Us	-2.09	1.95
Ua	-.98	1.73
Uv	-.72	1.92

N = 28
Notes: Ns — No threat, somatosensory modality; Na — No threat, auditory modality; Nv — No threat, visual modality; Ps — Predictable, somatosensory modality; Pa — Predictable, auditory modality; Pv — Predictable, visual modality; Us — Unpredictable, somatosensory modality; Ua — Unpredictable, auditory modality; Uv — Unpredictable, Visual modality.

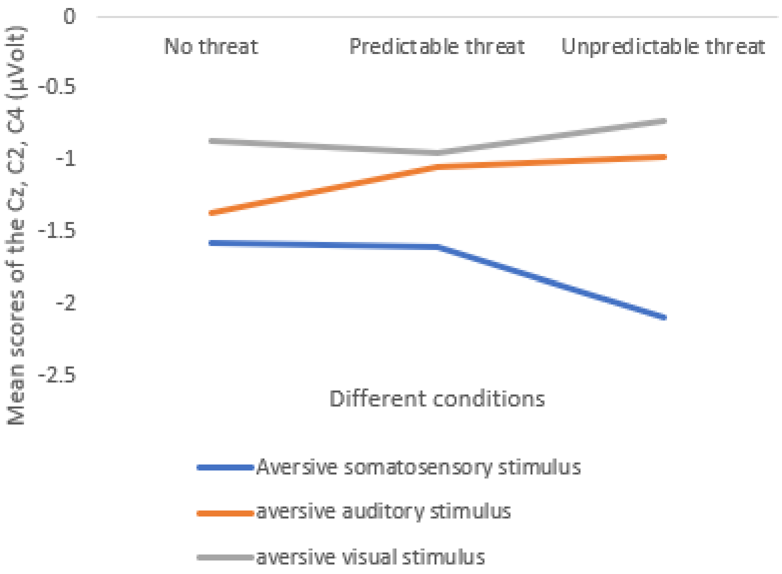


Figure 3.04. Scores of the N1 component in neutral somatosensory stimulus presented with threat in all three modalities and with all three conditions.

Figures below display N1 waveforms in all three conditions with the neutral somatosensory stimulus in different threat modalities (visual, somatosensory, auditory). Enhancement of the N1 component in the unpredictable condition with the somatosensory threat is clearly visible.

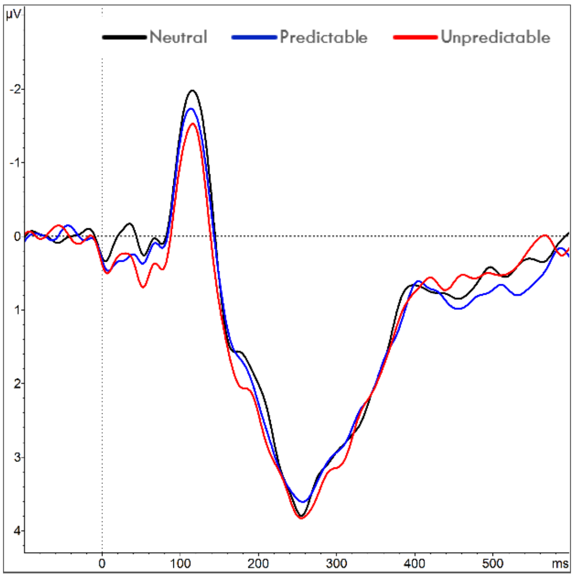


Figure 3.05. The N1 component in the auditory threat.

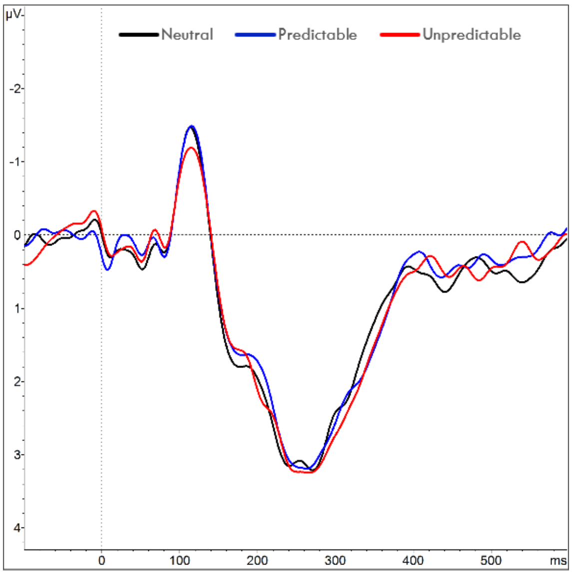


Figure 3.06. The N1 component in the visual threat.

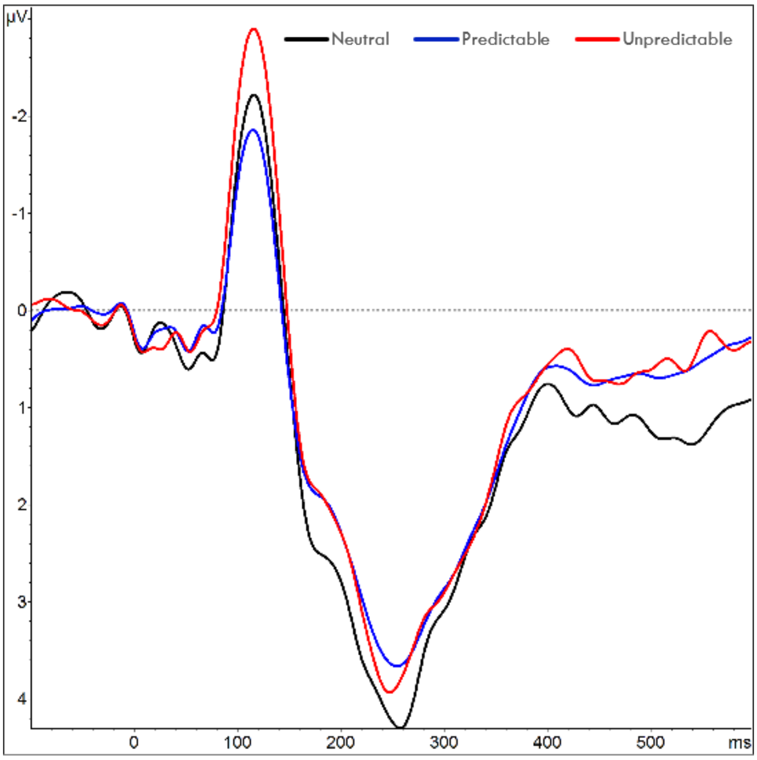


Figure 3.07. The N1 component in the somatosensory threat.

3.3 The correlations of questionnaires and ERPs

Table 3.04 presents correlations between the results of the BDI and STAI with the averaged Cz, C2, and C4 difference scores between different conditions in the somatosensory modality.

The results revealed no correlation between the BDI, STAI, and the N1 enhancement.

Table 3.04
Correlations between the BDI, STAI and the N1 enhancement in the somatosensory modality

		Unpredictable and no threat	Predictable and no threat	Unpredictable and predictable
BDI	Pearson Correlation	-.03	.08	-.12
	Sig. (2-tailed)	.88	.70	.55
	N	28	28	28
State Anxiety Sum	Pearson Correlation	.15	.28	-.15
	Sig. (2-tailed)	.45	.15	.45
	N	28	28	28
Trait Anxiety Sum	Pearson Correlation	.29	.28	.01
	Sig. (2-tailed)	.13	.15	.94
	N	28	28	28

4 DISCUSSION

The aim of this study was to investigate the influence of threat anticipation on sensory responses in the visual, auditory, and somatosensory modalities. We analyzed the N1 component when neutral stimuli were presented and compared the amplitudes of different modalities in the no threat, predictable threat, and unpredictable threat conditions. We took ratings of the neutral and aversive stimuli before and after the three blocks of different threat modality to distinguish between different ranges of their intensity and unpleasantness and to observe whether habituation was present. We also checked for any possible correlation between the BDI, STAI results and the N1 enhancement to see if there was any interference with our results.

As we did not find the N1 enhancement in any of the three modalities in the unpredictable condition, we can dismiss our first hypothesis along with the second supramodal hypothesis. We did not find a significant effect on the N1 amplification in the visual modality while anticipating the unpredictable threat, indicating that hypervigilance did not occur. A possible explanation would be that in contrast to shock, which presents a source of actual physical threat, the aversive picture represents a mere visual threat (Lissek et al., 2007). It is noteworthy that some potential effects of habituation were present in the ratings of the stimuli, specifically that the aversive visual stimulus appeared less unpleasant after the three blocks. Such habituation is commonly observed if emotional stimuli are repeated over successive trials (Plichta et al., 2014). There was also no significant effect on the N1 amplification in the auditory modality while anticipating the unpredictable threat, however the interaction between threat condition and the auditory modality was barely insignificant. This could be explained by a fairly small sample of 28 participants. A larger sample would provide more trials, which could lead to better signal-to-noise ratios (Dieterich et al., 2016). The stimuli ratings also show that the aversive auditory stimulus appeared more unpleasant and intense than the aversive somatosensory and visual stimuli, supporting the notion that significant results would be possible with a larger sample.

The results showed that only anticipating an unpredictable aversive somatosensory stimulus had a significant effect on sensory responses to neutral somatosensory stimuli. This is evident from the significant interaction between threat modality and condition. Shocks appear to be a more potent elicitor of vigilance mode (Shackman et al., 2011), a state in which N1 amplification can be observed due to the modulation of extrastriate cortex by the amygdala (Bzdok et al., 2013; Lim, Padmala and Pessoa, 2009). This supports the notion of a heightened vigilance to somatosensory stimuli while anticipating a somatosensory threat. Because there was a significant effect on sensory responses to neutral stimuli in the condition where threat was of the same modality, we can partially confirm the third, intramodal hypothesis, concerning the notion of a sensory-specific brain organization according to function (Driver and Noesselt, 2007). However, this should be considered with caution since source localization remains imperfect with EEG (Woodman, 2010) and we are witnessing a growing body of literature on the emerging consensus that multisensory effects can influence traditional "sensory-specific" regions (Driver and Spence, 2000; Frassinetti, Bolognini and Làdavas, 2002; Lovelace, Stein and Wallace, 2003; Macaluso, 2006; McDonald, Teder-Salejarvi, and Hillyard, 2000; Vroomen and Gelder, 2000). Our results are somewhat inconsistent with previous findings. Domínguez-Borràs and colleagues (2017) posit that emotional processing is similar to attentional processes that modulate early modality-specific neural responses across the visual, auditory, and somatosensory cortices, thereby extending the crossmodal hypothesis. They observed functional connectivity as an increase in activity in areas responsible for auditory and somatosensory information processing that was concurrent with a decrease in areas responsible for visual information processing when participants were presented with fearful faces. The difference in our results could be attributed to spatial proximity between stimuli in the study by Domínguez-Borràs (all the stimuli were near the subjects' head), which is known to influence crossmodal attention (Driver and Spence, 2000). That was not the case in our study since none of our stimuli were close to the subjects' head. There is an increasing body of literature supporting brain connectivity, especially the functional connectivity, which postulates temporal dependency of neuronal activation patterns of anatomically separated brain regions (Lang et al., 2012). The fact that we did not observe crossmodal, functional connectivity does not exclude the latter, but rather highlights the limitations of our study, described below.

Our results showed no sensory competition between auditory, visual, and somatosensory modalities, which is why we were able to observe independent, modality-specific attentional processing, but not functional connectivity (Rapp and Hendel, 2003). With this in mind we can, again, partially confirm our intramodal hypothesis. Domínguez-Borràs and colleagues (2017) observed a mechanism of sensory competition through a decrease in primary visual cortex due to concomitant processing of emotional faces and irrelevant visual stimuli, however these findings are inconsistent with our own. It should be noted that peripheral distractors and emotional faces appeared concurrently, whereas the stimuli presented in our study were nonconcurrent. A possible explanation would be the unequal aversiveness of our stimuli. Neutral conditions may appear more salient in a threatening environment (Domínguez-Borràs et al., 2017) and it could be that some of our aversive stimuli were not threatening enough. We cannot conclude, however, that different types of aversive stimuli produce comparable attentional engagement (Nelson and Hajcak, 2017), due to the fact that we observed the N1 enhancement only in one sensory modality. Note that sensory competition implicates both the low-level sensory systems and the high-level fronto-sensorimotor networks. A study done by Huang et al. (2015), investigating the multisensory competition in the sensory pathway interactions with fronto-sensorimotor and default-mode network (DMN) regions, presented their participants simultaneously with visual and auditory targets. They found increased prestimulus activity in the prefrontal cortex and decreased prestimulus activity in the DMN, which enhanced visual dominance over auditory modality while exploiting the fMRI. The DMN is a concept that describes a resting state activity in which an individual is awake and alert, but not actively involved in an attention-demanding or goal-directed task. The network includes precuneus/posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), and medial, lateral, and inferior parietal cortex (Lang et al., 2012). Huang et al. (2015) also observed that the ERPs and the divergence between the two conditions began to reach significance at 250 ms after the onset of the target. A possible explanation why we did not observe any sensory competition could therefore be our choice of method as the DMN network was more difficult to observe with the electrodes we chose. We also focused on the N1 component that peaks at approximately 100 ms.

As mentioned, a probable explanation for our results could also be our choice of electrodes. The fact that the right hemisphere is involved in vigilance and arousing states of anxiety is well documented (Shackman et al., 2011; Petersen and Posner, 1990). For example, in their study, Shackman et al. (2011), used a sophisticated method of determining the most stress-sensitive scalp regions where they chose a large cluster of electrodes centred along fronto-central part of the scalp and in the vicinity of the right mastoid. States of stress elicited by threat of shock and aversive images potentially activate the right lateral prefrontal cortex (Coan, Schaefer and Davidson, 2006; Dalton, Kalin, Grist and Davidson, 2005; Dolcos, 2006). A study done by Gilmore, Clementz, and Berg (2009) specifically investigated hemispheric laterality and ERP components. The results showed consistently stronger target-specific cortical activity in right temporal and parietal areas when the participants performed the auditory oddball paradigm binaurally and monaurally. The N1 component occurs only at 80–100 ms post stimulus, which is why it is very important to choose the right electrode (Woodman, 2010). It could be that we did not get more significant results because our electrodes were mainly positioned around the central site of the scalp.

There are other factors that could interfere with our results. For example, the results of the BDI and STAI questionnaires showed that all our participants were in the normal range. There was no correlation between the results of the questionnaires and different scores of the N1 component between different conditions, indicating that the final average scores of the N1 component were not influenced by the symptoms of anxiety or depression.

Furthermore, the participants took a test after the three blocks where they had to indicate the probability of a threat occurring after each cue. This test served as a verification whether they understood the meaning of cues throughout the experiment, which was important to differentiate between the three different conditions. The results indicated that the majority accurately followed cues throughout the experiment, while some did not. One participant indicated that the probability of a threat occurring after the predictable cue was 50%, four participants indicated the wrong probability of a threat occurring after the unpredictable cue, and six participants indicated the wrong probability of a threat occurring in the safe condition. These participants misunderstood the cues and it could be they were not paying close attention to the experiment, which could have interfered with our results by diminishing the number of validate trials.

The present study has several limitations that should be taken into consideration. First, the generalizability of the results to other populations (such as children or clinical populations) is questionable due to the fact that the sample consisted of college undergraduates. Second, a small sample size, as was the case with our experiment, has low statistical power, whereas a larger sample could produce more significant results overall. Third, our study contained disproportionate aversiveness of different stimuli and threats therefore did not appear threatening on the same level. Another possible limitation could be the environment of the experiment—a laboratory, located at the university where participants study, an environment that is familiar to them and overall safe. Furthermore, the experiment was always led by two of our team, students as well, meaning that the participants had a sense of shared social identity. The results of the state anxiety were also within normal range. These factors could have attenuated the threats that consequently simply did not appear "threatening enough". Future studies should involve equally threatening stimuli and strive to use stimuli on a similar level of arousal, as it is well known that arousal drives attention potentially captured by ERP components (Cuthbert et al., 2000; Schupp, Cuthbert, Bradley, Cacioppo, Ito and Lang, 2000; Schupp, Stockburger, Codispoti, Junghofer, Weike and Hamm, 2007; Weinberg and Hajcak, 2010). Considering the above, a more appropriate design for future studies would be to conduct them individually with separate modalities and use a homogenous category of stimuli within the same modality. This is especially plausible when the NPU-threat task is used to reduce the element of uncertainty during the predictable threat condition (Nelson et al., 2015). Nonetheless, our results add to the growing number of studies that use the NPU-threat task, indicating that measures of attention during the NPU-threat task have valuable psychometric properties.

5 CONCLUSIONS

Sensory processing in a hypervigilant state, i.e. when an individual experiences increased attention to a possible threat in the environment, is still not completely understood. The present study aimed to examine sensory processing during anticipation of predictable and unpredictable threats in the auditory, visual, and somatosensory modalities. We were interested in neural responses to neutral stimuli preceding threat. Furthermore, we focused on three modalities to see if the processes are selectively influenced in the course of anticipating threat. This study sought to contribute to a better understanding of hypervigilance and thereby expand our knowledge of the anxious state.

The results showed the N1 enhancement in the unpredictable condition in the somatosensory modality. Sensory responses to neutral stimuli were enhanced when presented with the unpredictable threat of shock. These results imply that an individual goes into a hypervigilant state when there is a possibility of a somatosensory threat in the environment. We did not observe any presence of sensory competition, meaning that processes were not selectively influenced. As we detected an enhanced N1 in the neutral stimuli that was of the same modality as the aversive threat, we can confirm the intramodal hypothesis that suggests a sensory-dependent attentional activity.

This is somewhat inconsistent with previous findings. In recent years, crossmodality, along with functional connectivity of the brain, has been studied to a considerable degree. However, it is possible that with a larger sample we would also observe the N1 enhancement in the auditory modality, as the results were barely insignificant. Overall, future studies should focus on a larger sample and a modality-specific design of the study in combination with a homogenous category of stimuli, which could produce findings that would be more consistent with recent literature.

Nevertheless, the present study contributes to the growing body of literature on how unpredictable threat leads to a more sustained level of anxiety, producing a state of increased attention to stimuli that would otherwise appear non-threatening. A better understanding of the origin of unpredictability and its consequences could provide clues to identifying unpredictability as a causal factor in the development of anxiety.

6 POVZETEK V SLOVENŠČINI

6.1 Uvod

V preteklih letih se je veliko študij usmerilo k raziskovanju senzoričnega procesiranja groženj v upanju, da bi bolje razumeli mehanizme simptomov anksioznosti, kjer pri posamezniku pogosto nastopi stanje hipervigilance. Še vedno ni popolnoma jasno, kako možgani v tem stanju obdelajo vhodne informacije, še posebej pa kako različne senzorične modalitete medsebojno interagirajo. Grožnje iz okolja so lahko predvidljive ali nepredvidljive in način, kako se na njih odzovemo, lahko postane ključnega pomena za naše preživetje. Nepredvidljive grožnje navadno povzročajo anksioznost, značilnost katere je hipervigilanca, medtem ko neizbežne, predvidljive grožnje povzročajo strah (Grillon idr., 2004).

Dognanja nedavnih študij nakazujejo, da nevarno okolje poveča občutljivost in reaktivnost na dražljaje v vseh senzoričnih modalitetah (Baas idr., 2007; Dunning idr., 2013; Sharvit idr., 2016), vendar je še vedno nejasno, ali v trenutku pred grožnjo pozornost in senzorične modalitete interagirajo intramodalno, krosmodalno ali supramodalno (Cecchetti idr., 2016; Dieterich idr., 2016; Domínguez-Borràs idr., 2017; Driver in Noesselt, 2008). V tej študiji smo se zato osredotočili raziskati, kako točno anksioznost vpliva na procesiranje senzoričnih informacij v treh različnih senzoričnih modalitetah, ko pričakujemo predvidljive ali nepredvidljive grožnje.

V študiji smo izkoristili odlično časovno ločljivost, ki jo ponujajo dogodkovni potenciali (ERP-ji). Elektroencefalografija (EEG) in ERP-ji merijo električne potenciale, ki so generirani v zunajcelični tekočini v obliki ionov, ki jih lahko opazimo, ko se nevtrotransmiterji prenašajo po celičnih membranah. Generira jih post-sinaptični potencial kortikalnih piramidalnih celic. S pomočjo ERP-jev lahko kognitivne operacije vizualiziramo z opazovanjem pozitivnih in negativnih amplitud. Specifične pozitivne in negativne amplitude, ki se zgodijo po točno določenem času po predstavitvi dražljaja, lahko označimo kot ERP komponente. Ostale značilnosti ERP komponent poleg polarnosti so čas, distribucija po skalpu in občutljivost na specifičnost nalog. Specifična komponenta se nanaša na kognitivne procese in možgansko aktivnost, ki jih lahko opazimo preko potenciala (Woodman, 2010).

V naši študiji smo se osredotočili na komponento N1 pri nevtralnih dražljajih v pričakovanju predvidljive in nepredvidljive grožnje v zvočni, vizualni in somatosenzorni modaliteti. Želeli smo raziskati, ali bo stanje hipervigilance vplivalo na pozornost, usmerjeno proti nevtralnim dražljajem v vseh modalitetah ali samo v eni. Želeli smo opazovati ali bo med pričakovanjem grožnje prišlo do selektivnega vpliva na procesiranje. Na podlagi tega smo oblikovali tri hipoteze.

H1: Hipervigilanca bo med pričakovanjem nepredvidljive grožnje prisotna v vseh treh senzoričnih modalitetah, kar bomo opazili kot ojačanje komponente N1.

H2: Ojačanje komponente N1 v vseh treh senzoričnih modalitetah med pričakovanjem nepredvidljive grožnje bo pomenilo, da smo opazili supramodalnost oz. senzorično neodvisno aktivnost.

H3: Ojačanje komponente N1 pri nevtralnih dražljajih enake senzorične modalitete kot senzorična modaliteta grožnje bo pomenilo, da smo opazili intramodalnost oz. možgansko aktivnost, ki je senzorično odvisna od modalitete.

6.2 Metode

6.2.1 Vzorec

V študiji so sodelovali dodiplomski študentje (demografske podatke udeležencev je možno razbrati iz Tabele 2.01) iz Univerze Erasmus v Rotterdamu, ki so v zameno za sodelovanje dobili kreditne točke pri določenem predmetu. Vsi so podpisali soglasje o sodelovanju pri raziskavi (priloga A). Podatke ene izmed udeleženk nismo vključili, saj je želela eksperiment končati predčasno, ker se je počutila preveč anksiozno, tako da smo na koncu imeli 28 udeležencev. Raziskavo je odobrila etična komisija Erasmus univerze.

6.2.2 Pripomočki

Za slušni nevtralni dražljaj smo uporabili piskajoč zvok s frekvenco 500 Hz. Za averzivni slušni dražljaj smo uporabili ženski krik pri 90 dB. Za vizualni averzivni dražljaj smo iz International Affective Pictures System (IAPS; Lang et al. 2008) izbrali sliko umorjenega moškega (Slika 2.01). Za vizualni nevtralni dražljaj smo izbrali sliko presevajoče svetlobe skozi rešetke (Slika 2.01). Slike in znaki situacij so bili velikosti 500 x 500 pikslov. Za somatosenzorni averzivni in nevtralni dražljaj smo uporabili električno stimuliranje mišice na levi roki, ki je bilo prilagojeno posameznikovemu pragu bolečine. Nevtralni in averzivni dražljaj sta se med sabo ločila po dolžini trajanja (opisano v Postopku).

V študiji smo uporabili dva vprašalnika – State-Trait Anxiety Inventory (Spielberger et al., 1983) in Beck Depression Inventory (Beck, 1961). Po koncu eksperimenta so udeleženci morali rešiti še test, s katerim smo preverili razumevanje posameznih znakov tekom eksperimenta (priloga B).

Pri snemanju EEG-ja smo uporabili 64 srebro-srebrokloridnih (Ag/AgCl) elektrod, nameščenih na standardne položaje po mednarodnem sistemu 10/20 (Oostenveld in Praamstra, 2001). Elektrookulogram je bil posnet s štirimi dodatnimi elektrodami – dve sta bili nameščeni približno 1 cm zunanje od levega in desnega očesa ter dve približno 1 cm nad in pod levim očesom. Podatki so bili posneti z uporabo BioSemi ActiveTwo ojačevalca, s filtrom z vrednostjo 134 Hz, gostoto vzorčenja 512 Hz oz. 512 vzorcev na sekundo in 24-bitno analogno/digitalno pretvorbo. BioSemi uporablja »common mode sense« (CMS) in elektrode, da ustvari povratno zanko, ki nadomešča običajno ozemljitveno elektrodo.

6.2.3 Postopek

Udeleženci so najprej prebrali in podpisali soglasje, nato pa so na računalniku rešili vprašalnika STAI in BDI, kar je trajalo približno 10 minut. Eksperiment se je nadaljeval v izolirani sobi, kjer je potekalo snemanje EEG-ja. Izmerili smo obseg glave, da smo za vsakega udeleženca lahko izbrali primerno kapo z elektrodami. Nato smo za boljšo prevodnost aplicirali gel na vsako elektrodo. Ko smo opravili z nameščanjem EEG-ja, smo začeli z izračunom bolečinskega praga, s čimer smo določili intenziteto elektrošoka. Uporabili smo električni dražljaj s frekvenco 50 Hz, proizveden s stalni tokom stimulatorja (Digitimer DS7A, Digitimer LTD., Welwyn Garden City, UK). Pred postopkom merjenja praga bolečine je bila udeležencem predstavljena lestvica od 0 do 10, kjer je stopnja 4 označevala »komaj zaznano bolečino«. Tekom postopka se je intenziteta šoka postopoma višala ter nižala. Začeli smo z 0 mA ter vsakič, ko je udeleženec šok ocenil s 4, zamenjali smer (nižanje ali višanje intenzitete). Stopnja se je vsakič zvišala ali znižala za 1 mA. Da smo določili prag bolečine, smo vzeli vse meritve, ocenjene s 4, in izračunali povprečje, kateremu smo nato dodali 30 % (priloga C). Električna stimulacija je bila tekom tega postopka vedno aplicirana za 2 ms. Povprečje intenzitete šoka celotnega vzorca je bilo 2,34 mA (*SD* = 1,65) in ocena 5,72 (*SD* = 0,97).

Nato smo udeležencem razložili kaj vsak znak pomeni in kolikšna je verjetnost grožnje (priloga D). Sledilo je ocenjevanje nevtralnih in averzivnih dražljajev. Na ekranu se je udeležencem prikazalo vprašanje »Kako intenziven se vam zdi dražljaj?«, kateremu je sledila predstavitev vsakega izmed uporabljenih dražljajev v eksperimentu. Postopek se je ponovil še za vprašanje »Kako neprijeten se vam zdi dražljaj?«. Udeležencem je bila za vsak dražljaj predstavljena digitalna lestvica, razpon katere je bil od -50 skrajno levo (najmanj neprijetno ali intenzivno) do 50 skrajno desno (najbolj neprijetno ali intenzivno).

Z miško so izbrali ustrezno stopnjo in s tem določili oceno. Ocene smo zbrali pred in po eksperimentu.

Po ocenah smo začeli z NPU-threat task (Schmitz in Grillon, 2012). Udeleženci so opravili tri bloke naloge, vsak blok z eno od treh modalitet grožnje. Grožnje so predstavljali averzivni dražljaji – ženski krik, slika umorjenega moškega in dolg elektrošok. Bloki so bili tekom eksperimenta med vsemi udeleženci uravnoteženi in so si sledili v naslednjem zaporedju: 123, 231 ali 312.

Slika 2.05 predstavlja shematičen prikaz eksperimentalnega poskusa. Trikotnik, krog in diamant predstavljajo znake situacij, bele ikone nevtralne dražljaje, rdeče ikone pa averzivne. V situaciji brez grožnje (trikotnik) ni bilo nobenega averzivnega dražljaja, le prazen, črn ekran. V situaciji s predvidljivo grožnjo (krog) je bil s 100-odstotno verjetnostjo predstavljen averzivni dražljaj, modaliteta katerega je bila odvisna od bloka. V nepredvidljivi situaciji (diamant) je bila grožnja predstavljena s 50-odstotno verjetnostjo. V primerov je bil predstavljen averzivni dražljaj (modaliteta je bila odvisna od bloka), v 50 % primerov pa prazen, črn ekran.

Vsaka NPU situacija je vsebovala 20 poskusov, kar je na koncu naneslo na skupno 540 poskusov, 180 poskusov za vsak blok in 60 za vsako situacijo. Poskus se je začel s fiksirajočim križem, kateremu je sledil znak, ki je nakazoval situacijo. Nato je sledil eden izmed treh nevtralnih dražljajev, ki je bil predstavljen trikrat. Na koncu poskusa se je prikazal črn, prazen ekran ali pa averzivni dražljaj (grožnja). Celoten eksperimentalni program z vsemi tremi bloki je trajal približno 50 minut.

Slika 2.06 nam nakaže časovno trajanje poskusa. Znaki, ki so nakazovali situacijo, so trajali 500 ms. Nevtralni vizualni in zvočni dražljaj sta trajala 200 ms in sta bila ponovljena trikrat (3-krat 200 ms) z intervalom med dražljaji (1000–2000 ms). Nevtralni somatosenzorni dražljaj je trajal 2 ms. Averzivni vizualni in zvočni dražljaj sta trajala 2000 ms. Averzivni somatosenzorni dražljaj je skupno trajal 40 ms (10-krat 2 ms z vmesnimi premori 2 ms).

Po koncu treh blokov so udeleženci še enkrat ocenili nevtralne in averzivne dražljaje glede na njihovo intenzivnost in neprijetnost. Po koncu celotnega eksperimenta so udeleženci prejeli še kratek test preverjanja znakov, kjer so morali zabeležiti, s kolikšno verjetnostjo je po vsakem predstavljenem znaku sledila grožnja. Celoten eksperiment je trajal približno 2 uri.

6.3 Rezultati

6.3.1 Ocene dražljajev

Model ANOVE za ponovljene meritve z uporabo znotrajosebnih (within-subject) faktorjev 2 (*nevtralni, averzivni dražljaji*) x 3 (*vizualna, zvočna in somatosenzorna modaliteta*) na ocenah intenzitete dražljajev $F(2,54) = 11,55$, $p < ,001$ in neprijetnosti dražljajev $F(2,54) = 14,73$, $p < ,001$ je pokazal značilen učinek averzivnega zvočnega dražljaja. Izkazal se je za bolj neprijetnega in intenzivnega od averzivnega somatosenzornega in vizualnega dražljaja. Rezultati so vidni v Sliki 3.01 in Sliki 3.02 ter Tabeli 3.01 in Tabeli 3.02.

Model ANOVE za ponovljene meritve z uporabo znotrajosebnih faktorjev 2 (*pred eksperimentom in po eksperimentu*) x 2 (*nevtralni, averzivni dražljaji*) x 3 (*vizualna, zvočna in somatosenzorna grožnja*) ocen dražljajev je pokazal značilen rezultat za averzivni vizualni dražljaj, ki je bil manj neprijeten po koncu treh blokov in za averzivni zvočni dražljaj, ki je bil bolj neprijeten po eksperimentu $F(2,54) = 4,45$, $p = ,016$. Rezultati so prikazani v Sliki 3.03.

6.3.2 Vrednosti komponente N1

Rezultati ANOVE za ponovljene meritve z znotrajosebnim faktorjem 3 (*brez grožnje, predvidljiva grožnja, nepredvidljiva grožnja*) x 3 (*zvočna, vizualna in somatosenzorna grožnja*) niso pokazali značilnega učinka ampak značilno interakcijo med averzivnim vizualnim dražljajem in averzivnim somatosenzornim dražljajem v nepredvidljivi situaciji $F(4,108) = 2,92$, $p = ,024$. Ostali rezultati mešane ANOVE na drugih dveh modalitetah niso pokazali značilnih učinkov ali interakcij.

V Tabeli 3.03 vidimo vrednosti povprečij elektrod Cz, C2 in C4 za nevtralne somatosenzorne dražljaje v vseh treh situacijah in vseh treh modalitetah.

Zaradi omenjene značilne interakcije smo izvedli t test, da bi raziskali povezavo. Povezava med situacijo brez grožnje in situacijo z nepredvidljivo grožnjo je pokazala značilne rezultate $t(27) = 2,39$, p ,024, kot tudi povezava med situacijo brez grožnje in situacijo s predvidljivo grožnjo $t(27) = 2.47$, p ,02.

6.4 Sklepi

Naši rezultati so pokazali ojačanje komponente N1 za somatosenzorne nevtralne dražljaje v situaciji z nepredvidljivo grožnjo elektrošoka. Med različnimi modalitetami nismo opazili senzorične tekmovalnosti, kar pomeni, da ni prišlo do selektivnega vpliva na procese. Ker smo ojačanje komponente N1 opazili pri nevtralnih dražljajih enake modalitete kot grožnje, lahko delno potrdimo našo intramodalno hipotezo, ki predpostavlja, da je možganska aktivnost odvisna od senzorične modalitete. S pomočjo ocen dražljajev pred in po eksperimentu smo opazili prisotnost habituacije v primeru vizualne modalitete, kar bi lahko vplivalo na pridobljene vrednosti N1.

Naši rezultati se ne ujemajo povsem z dognanji prejšnjih študij, ki se nagibajo v smer krosmodalnosti ter funkcijske možganske povezljivostji. Obstaja možnost, da ojačanja N1 v zvočni modaliteti nismo opazili zaradi premajhnega vzorca – rezultati zvočne modalitete so bili namreč skoraj značilni. Bodoče študije bi se lahko osredotočile na večji vzorec ter oblikovale eksperimente, ki bi se fokusirali na eno modaliteto in uporabili homogeno kategorijo dražljajev.

7 REFERENCES

Baas, J., Milstein, J., Donlevy, M. and Grillon, C. (2006). Brainstem Correlates of Defensive States in Humans. *Biological Psychiatry, 59(7),* 588-593.

Bandettini, P. (2012). Twenty years of functional MRI: The science and the stories. *Neuroimage, 62(2*), 575-588.

Barlow, D. (2000). Unraveling the mysteries of anxiety and its disorders from the perspective of emotion theory. *American Psychologist, 55(11),* 1247-1263.

Beck, A. (1961). An Inventory for Measuring Depression. *Archives of General Psychiatry, 4(6),* 561.

Berens, A., Jensen, S. and Nelson, C. (2017). Biological embedding of childhood adversity: from physiological mechanisms to clinical implications. *BMC Medicine, 15(1).*

Bidet-Caulet, A., Barbe, P., Roux, S., Viswanath, H., Barthélémy, C., Bruneau, N., Knight, R. and Bonnet-Brilhault, F. (2012). Dynamics of anticipatory mechanisms during predictive context processing. *European Journal of Neuroscience, 36(7),* 2996-3004.

Bishop, S. (2007). Neurocognitive mechanisms of anxiety: an integrative account. *Trends in Cognitive Sciences, 11(7),* 307-316.

Bzdok, D., Laird, A., Zilles, K., Fox, P. and Eickhoff, S. (2012). An investigation of the structural, connectional, and functional subspecialization in the human amygdala. *Human Brain Mapping, 34(12),* 3247-3266.

Cecchetti, L., Kupers, R., Ptito, M., Pietrini, P. and Ricciardi, E. (2016). Are Supramodality and Cross-Modal Plasticity the Yin and Yang of Brain Development? From Blindness to Rehabilitation. *Frontiers in Systems Neuroscience, 10.*

Coan, J., Schaefer, H. and Davidson, R. (2006). Lending a Hand: social regulation of the neural response to threat. *Psychological Science, 17(12),* 1032-1039.

Cornwell, B., Baas, J., Johnson, L., Holroyd, T., Carver, F., Lissek, S. and Grillon, C. (2007). Neural responses to auditory stimulus deviance under threat of electric shock revealed by spatially-filtered magnetoencephalography. *NeuroImage, 37(1),* 282-289.

Cuthbert, B., Schupp, H., Bradley, M., Birbaumer, N. and Lang, P. (2000). Brain potentials in affective picture processing: covariation with autonomic arousal and affective report. *Biological Psychology, 52(2),* 95-111.

Dalton, K., Kalin, N., Grist, T. and Davidson, R. (2005). Neural-Cardiac Coupling in Threat-Evoked Anxiety. *Journal of Cognitive Neuroscience, 17(6),* 969-980.

Dedovic, K., Duchesne, A., Andrews, J., Engert, V. and Pruessner, J. (2009). The brain and the stress axis: The neural correlates of cortisol regulation in response to stress. *NeuroImage, 47(3),* 864-871.

Dieterich, R., Endrass, T. and Kathmann, N. (2016). Uncertainty is associated with increased selective attention and sustained stimulus processing. *Cognitive, Affective, & Behavioral Neuroscience, 16(3),* 447-456.

Dolcos, F. (2006). Brain Systems Mediating Cognitive Interference by Emotional Distraction. *Journal of Neuroscience, 26(7),* 2072-2079.

Domínguez-Borràs J., Walter Rieger S., Corradi-Dell’Acqua C., Neveu R. and Vuilleumier P. (2017). Fear Spreading Across Senses: Visual Emotional Events Alter Cortical Responses to Touch, Audition, and Vision. *Cerebral Cortex, 27,* 68–82.

Driver, J. and Noesselt, T. (2008). Multisensory Interplay Reveals Crossmodal Influences on ‘Sensory-Specific’ Brain Regions, Neural Responses, and Judgments. *Neuron, 57(1),* 11-23.

Driver, J. and Spence, C. (2000). Multisensory perception: Beyond modularity and convergence. *Current Biology, 10(20),* R731-R735.

Duncan, C., Barry, R., Connolly, J., Fischer, C., Michie, P., Näätänen, R., Polich, J., Reinvang, I. and Van Petten, C. (2009). Event-related potentials in clinical research: Guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clinical Neurophysiology, 120(11),* 1883-1908.

Dunning, J., DelDonno, S. and Hajcak, G. (2013). The effects of contextual threat and anxiety on affective startle modulation. *Biological Psychology, 94(1),* 130-135.

Felmingham, K. L., Stewart, L. F., Kemp, A. H., & Carr, A. R. (2016). The impact of high trait social anxiety on neural processing of facial emotion expressions in females. *Biological Psychology, 117,* 179–186.

Fernandes, V. and Osório, F. (2015). Are there associations between early emotional trauma and anxiety disorders? Evidence from a systematic literature review and meta-analysis. *European Psychiatry, 30(6),* 756-764.

Frassinetti, F., Bolognini, N. and Làdavas, E. (2002). Enhancement of visual perception by crossmodal visuo-auditory interaction. *Experimental Brain Research, 147(3),* 332-343.

Gilmore, C., Clementz, B. and Berg, P. (2009). Hemispheric differences in auditory oddball responses during monaural versus binaural stimulation. *International Journal of Psychophysiology, 73(3),* 326-333.

Godoy, L., Rossignoli, M., Delfino-Pereira, P., Garcia-Cairasco, N. and de Lima Umeoka, E. (2018). A Comprehensive Overview on Stress Neurobiology: Basic Concepts and Clinical Implications. *Frontiers in Behavioral Neuroscience, 12.*

Gorka, S., Lieberman, L., Shankman, S. and Phan, K. (2017). Startle potentiation to uncertain threat as a psychophysiological indicator of fear-based psychopathology: An examination across multiple internalizing disorders. *Journal of Abnormal Psychology, 126(1),* 8-18.

Gratton, G., Coles, M. and Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology, 55(4),* 468-484.

Grillon, C., Baas, J., Lissek, S., Smith, K. and Milstein, J. (2004). Anxious Responses to Predictable and Unpredictable Aversive Events. *Behavioral Neuroscience, 118(5),* 916-924.

Grosso, A., Santoni, G., Manassero, E., Renna, A. and Sacchetti, B. (2018). A neuronal basis for fear discrimination in the lateral amygdala. *Nature Communications, 9(1).*

Grupe, D. and Nitschke, J. (2013). Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. *Nature Reviews Neuroscience, 14(7),* 488-501.

Heimler, B., Striem-Amit, E. and Amedi, A. (2015). Origins of task-specific sensory-independent organization in the visual and auditory brain: neuroscience evidence, open questions and clinical implications. *Current Opinion in Neurobiology, 35,* 169-177.

Huang, S., Li, Y., Zhang, W., Zhang, B., Liu, X., Mo, L. and Chen, Q. (2015). Multisensory Competition Is Modulated by Sensory Pathway Interactions with Fronto-

Sensorimotor and Default-Mode Network Regions. *Journal of Neuroscience, 35(24),* 9064-9077.

Janak, P. and Tye, K. (2015). From circuits to behaviour in the amygdala. *Nature, 517(7534),* 284-292.

Joëls, M. and Baram, T. (2009). The neuro-symphony of stress. *Nature Reviews Neuroscience, 10(6),* 459-466.

Kimble, M., Boxwala, M., Bean, W., Maletsky, K., Halper, J., Spollen, K. and Fleming, K. (2014). The impact of hypervigilance: Evidence for a forward feedback loop. *Journal of Anxiety Disorders, 28(2),* 241-245.

de Kloet, E., Joëls, M. and Holsboer, F. (2005). Stress and the brain: from adaptation to disease. *Nature Reviews Neuroscience, 6(6),* 463-475.

Krauzlis, R., Bogadhi, A., Herman, J. and Bollimunta, A. (2018). Selective attention without a neocortex. *Cortex, 102,* 161-175.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2008*). International Affective Picture System (IAPS): Affective ratings of pictures and instruction manual (Technical Report No. A-8)*. Gainesville, FL: University of Florida, Center for Research in Psychophysiology.

Lang, E.W., Tome, A. M., Keck, I. R., Gorriz-Saez, J.M. and Puntonet, C. G. (2012). Brain Connectivity Analysis: A Short Survey. *Computational Intelligence and Neuroscience (12).*

LeDoux, J. (2000). Emotion Circuits in the Brain. *Annual Review of Neuroscience, 23(1),* 155-184.

Lim, S., Padmala, S. and Pessoa, L. (2009). Segregating the significant from the mundane on a moment-to-moment basis via direct and indirect amygdala contributions. *Proceedings of the National Academy of Sciences, 106(39),* 16841-16846.

Lindenberg, R. and Scheef, L. (2007). Supramodal language comprehension: Role of the left temporal lobe for listening and reading. *Neuropsychologia, 45(10),* 2407-2415.

Lissek, S., Orme, K., Mcdowell, D., Johnson, L., Luckenbaugh, D., Baas, J., Cornwell, B. and Grillon, C. (2007). Emotion regulation and potentiated startle across affective picture and threat-of-shock paradigms. *Biological Psychology, 76(1-2),* 124-133.

Lovelace, C., Stein, B. and Wallace, M. (2003). An irrelevant light enhances auditory detection in humans: a psychophysical analysis of multisensory integration in stimulus detection. *Cognitive Brain Research, 17(2),* 447-453.

Macaluso, E. (2006). Multisensory Processing in Sensory-Specific Cortical Areas. *The Neuroscientist, 12(4),* 327-338.

McDonald, J.J., Teder-Salejarvi, W.A., and Hillyard, S.A. (2000). Involuntary orienting to sound improves visual perception. *Nature 407*, 906–908.

Milad, M. and Quirk, G. (2012). Fear Extinction as a Model for Translational Neuroscience: Ten Years of Progress. *Annual Review of Psychology, 63(1),* 129-151.

Millett, D. (2001). Hans Berger: From Psychic Energy to the EEG. *Perspectives In Biology And Medicine, 44(4),* 522-542.

Miller, E. and Wallis, J. (2013). The Prefrontal Cortex and Executive Brain Functions. *Fundamental Neuroscience,* 1069-1089.

Nelson, B. and Hajcak, G. (2017). Defensive motivation and attention in anticipation of different types of predictable and unpredictable threat: A startle and event-related potential investigation. *Psychophysiology, 54(8),* 1180-1194.

Nelson, B., Hajcak, G. and Shankman, S. (2015). Event-related potentials to acoustic startle probes during the anticipation of predictable and unpredictable threat. *Psychophysiology, 52(7),* 887-894.

Niedermeyer, E. (1998). Frontal Lobe Functions and Dysfunctions. *Clinical Electroencephalography, 29(2),* 79-90.

Nieuwenhuis, S., Aston-Jones, G. and Cohen, J. (2005). Decision making, the P3, and the locus coeruleus--norepinephrine system. *Psychological Bulletin, 131(4),* 510-532.

Oostenveld, R. and Praamstra, P. (2001). The five percent electrode system for high-resolution EEG and ERP measurements. *Clinical Neurophysiology, 112(4),* 713-719.

Pezzulo, G. (2008). Coordinating with the Future: The Anticipatory Nature of Representation. *Minds and Machines, 18(2),* 179-225.

Plichta, M., Grimm, O., Morgen, K., Mier, D., Sauer, C., Haddad, L., Tost, H., Esslinger, C., Kirsch, P., Schwarz, A. and Meyer-Lindenberg, A. (2014). Amygdala habituation: A reliable fMRI phenotype. *NeuroImage, 103,* 383-390.

Posner, M. and Petersen, S. (1990). The Attention System of the Human Brain. *Annual Review of Neuroscience, 13(1)*, 25-42.

Posner, M. and Rothbart, M. (2007). Research on Attention Networks as a Model for the Integration of Psychological Science. *Annual Review of Psychology, 58(1),* 1-23.

Rapp, B. and Hendel, S. (2003). Principles of cross-modal competition: Evidence from deficits of attention. *Psychonomic Bulletin & Review, 10(1),* 210-219.

Rouby, Catherine & Fournel, Arnaud & Bensafi, Moustafa. (2016). *The Role of the Senses in Emotion*. 65-81.

Schmitz, A. and Grillon, C. (2012). Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). *Nature Protocols, 7(3),* 527-532.

Schupp, H., Stockburger, J., Codispoti, M., Junghofer, M., Weike, A. and Hamm, A. (2007). Selective Visual Attention to Emotion. *Journal of Neuroscience, 27(5),* 1082-1089.

Schupp, H., Cuthbert, B., Bradley, M., Cacioppo, J., Ito, T. and Lang, P. (2000). Affective picture processing: The late positive potential is modulated by motivational relevance. *Psychophysiology, 37(2),* 257-261.

Shackman, A., Maxwell, J., McMenamin, B., Greischar, L. and Davidson, R. (2011). Stress Potentiates Early and Attenuates Late Stages of Visual Processing. Journal of *Neuroscience, 31(3),* 1156-1161.

Sharvit, G., Vuilleumier, P., Delplanque, S. and Corradi-Dell’Acqua, C. (2016). Erratum: Erratum: Cross-modal and modality-specific expectancy effects between pain and disgust. *Scientific Reports, 6(1).*

Slotnick, S. D. (2004). Source localization of ERP generators. In T. C. Handy (Ed.), *EventRelated Potentials: A Methods Handbook* (149-166). Cambridge: The MIT Press.

Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

Stein, B., Stanford, T. and Rowland, B. (2009). The neural basis of multisensory integration in the midbrain: Its organization and maturation. *Hearing Research, 258(1-2),* 4-15.

Swartz, J., Knodt, A., Radtke, S. and Hariri, A. (2015). A Neural Biomarker of Psychological Vulnerability to Future Life Stress. *Neuron, 85(3),* 505-511.

Todd, R. and Manaligod, M. (2018). Implicit guidance of attention: The priority state space framework. *Cortex, 102*, 121-138.

Vroomen, J. and Gelder, B. (2000). Sound enhances visual perception: Cross-modal effects of auditory organization on vision. *Journal of Experimental Psychology: Human Perception and Performance, 26(5),* 1583-1590.

Weinberg, A. and Hajcak, G. (2010). Beyond good and evil: The time-course of neural activity elicited by specific picture content. *Emotion, 10(6),* 767-782.

Wise, V., McFarlane, A. C., Clark, C. R., & Battersby, M. (2009). Event-related potential and autonomic signs of maladaptive information processing during an auditory oddball task in panic disorder. *International Journal of Psychophysiology, 74,* 34–44.

Woodman, G. (2010). A brief introduction to the use of event-related potentials in studies of perception and attention. Attention*, Perception & Psychophysics, 72(8),* 2031-2046.

Xiong, F., and Zhang, L. (2013). Role of the hypothalamic-pituitary-adrenal axis in developmental programming of health and disease. *Front. Neuroendocrinol. 34,* 27–46.

Yang, J., Park, K., Eun, S., Lee, M., Yoon, J., Shin, I., Kim, Y., Chung, T., Kang, H. and Jeong, G. (2008). Assessment of Cerebrocortical Areas Associated with Sexual Arousal in Depressive Women Using Functional MR Imaging. *The Journal of Sexual Medicine, 5(3),* 602-609.

Zukerman, G., Fostick, L. and Ben-Itzchak, E. (2018). Early automatic hyperarousal in response to neutral novel auditory stimuli among trauma-exposed individuals with and without PTSD: An ERP study. *Psychophysiology, 13217.*

APPENDIX A
CONSENT FOR PARTICIPATION IN THE EXPERIMENT

STUDY INFORMATION “EXPECT THE UNEXPECTED!”

Dear participant,

Please read this document carefully before you decide to participate in this study. Before you consent, this document informs you about the purpose of the research study and what you will be asked in this study. If you have questions later, you can always contact the responsible researchers as stated below.

PURPOSE OF THIS RESEARCH STUDY:

The purpose of this research is to examine people’s responses when they anticipate a variety of different negative outcomes such as loud noise, aversive pictures, and electric stimulation.

What you will be asked to do in this study

In this study, you will be asked to view neutral pictures or listen to neutral sounds or feel low electrical stimulation while you wait for loud noise, aversive pictures, or electric stimulation. Your brain reactions will be recorded through EEG sensors. These sensors simply record the signals normally produced by your brain.

During this study, short (20 ms) electrical stimuli will be delivered to your lower arm. These stimuli are slightly painful, but very brief and absolutely not dangerous. The strength of these stimuli will be adjusted individually before the actual experiment. These stimuli may cause irritant sensations and very rarely some redness of your skin, which normally are very short-lived. If you find these stimulations uncomfortable, please tell the researcher.

The experiment lasts about 2 hours.

Benefits and risks

There are no direct benefits for you for taking part in this study. This study likely produces important scientific results, which will help us to understand better, how anxiety disorders develop and how they may be treated better. The risks involved in this study are minimal: Application of the sensors may in very rare cases cause skin irritations, such as short-lived redness. The loud sounds (screaming), aversive pictures (violence), and electrical stimulation may induce short-lived negative feelings. If any of the stimuli presented here should make you feel uncomfortable, you are free to immediately withdraw your participation and leave without giving up credit. There is a two-way communication system installed in the research room and you can discontinue the experiment at any time by simply telling the experimenter to stop.

Reimbursements

EUR students will receive course credits for participation.

Confidentiality

Your identity will be kept confidential to the extent provided by law. Records of this study will be kept in a confidential form at the institution. Your research records will include your answers to the questionnaires you fill out during the course of the study and the physiological recordings taken during the study. Your name will not appear on the questionnaires or be associated with your physiological recordings. If the results of this research are published or presented at scientific meetings, your identity will not be disclosed. This research was approved by the Institutional Review Board of the Erasmus University Rotterdam.

Voluntary participation

Your participation in this study is completely voluntary. There is no penalty for not participating. You have the right to withdraw from the study at any time without consequence.

More questions about the study?

Please contact the principal investigator, Prof. Dr. M.J. Wieser, Erasmus University Rotterdam.

STUDY “EXPECT THE UNEXPECTED!”

I confirm that I have read and understood the procedure described above. I was able to ask any question related to the study, and these were answered sufficiently. I know that my participation in this study is voluntary, and I may withdraw my consent at any time.

I voluntarily agree to participate in the aforementioned study.

Name participant :

Signature : Date : __ / __ / __

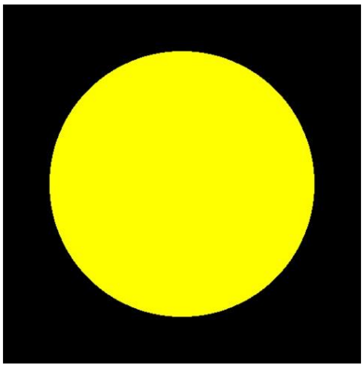
Name researcher :

Signature : Date : __ / __ / __

APPENDIX B
CUE VERIFICATION TEST

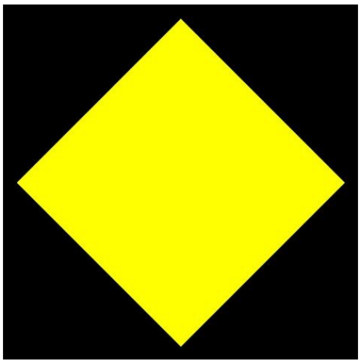
Subject ID: _______________

Please indicate the likelihood with which an aversive event occurred,
after you saw the respective object!
Remember: There was an aversive event in either 0%, 50%, or 100% of the cases after seeing the object. Please write the number under the respective object!



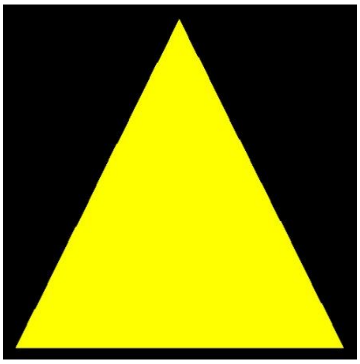
_______%

Likelihood of aversive event



_______%

Likelihood of aversive event



_______%

Likelihood of aversive event

APPENDIX C

PAIN-THRESHOLDING PROCEDURE

Research project:

Date: **Participant-Code:**

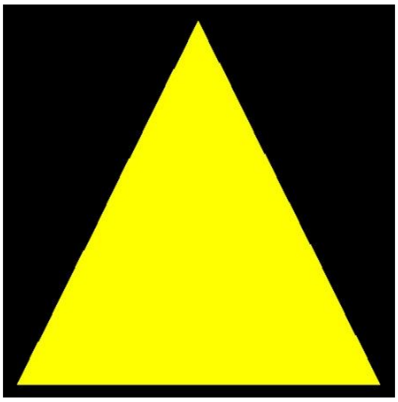
Pain Threshold Intensity

	Series1 UP	Series1 DOWN	Series2 UP	Series2 DOWN
8 mA				
7,5 mA				
7 mA				
6,5 mA				
6 mA				
5,5 mA				
5 mA				
4,5 mA				
4,0 mA				
3,5 mA				
3 mA				
2,5 mA				
2 mA				
1,5 mA				
1 mA				
0,5 mA				
0 mA				

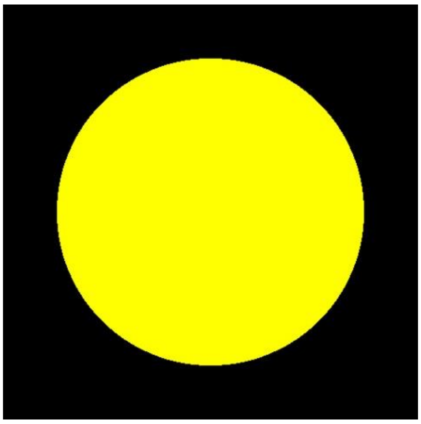
MEAN:______________________ (+ 30%)

Final Rating of intensity: ____________________

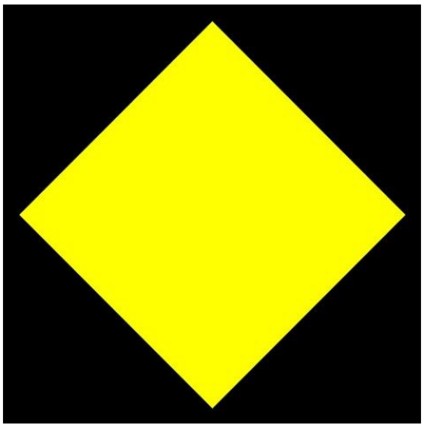
APPENDIX D
CONDITION DESCRIPTION WITH FIGURES



This is the safe condition! When you see this object, you are safe!
There is no unpleasant event for sure (100%)!



This is the 100% condition! When you see this object,
there is going to be an unpleasant event for sure (100%)!



This is the unpredictable condition! When you see this object,
there will be an unpleasant event with a 50% chance!